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CONTENTS

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A full summary of his observations and conclusions must be given.

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EDITORIAL

His Editorial colleagues and readers of the *Annals of the Rheumatic Diseases* will much regret to hear of Dr. Loring T. Swaim's wish to resign from the Editorial Committee owing to his retirement from active practice. The Editors place on record their great appreciation of the valuable services rendered by Dr. Swaim to rheumatology in general, and more particularly to the *Annals of the Rheumatic Diseases*. Dr. Swaim's interest and active support have for many years past helped to maintain the standard of the *Journal*, and his colleagues are very grateful for his assurance that this interest will continue after his retirement from active participation in Editorial matters.

Dr. Edward W. Boland of Los Angeles, California, who was chairman of the Programme Committee of the Seventh International Congress on Rheumatic Diseases held in New York last summer, and whose work in the rheumatic diseases will be well known to readers of the *Annals*, has been invited to fill the vacancy and has expressed his willingness to do so. The Editors look forward to Dr. Boland's co-operation in the work of the *Annals*, knowing that he will worthily sustain the high standard set by Dr. Swaim.

Authors submitting articles from America will facilitate the work of the Editors and also save time if they will send their articles in the first place to Dr. P. S. Hench at the Mayo Clinic, Rochester, Minnesota, or to Dr. E. W. Boland, 2210 West Third Street, Los Angeles 5, California, and not direct to the British Editors.

It has been found necessary, in view of the greatly increased cost of production, to raise the subscription to the *Annals* to 30s. per annum ($5 for the U.S.A.); single numbers will remain at 7s. 6d. These price changes will take effect with Volume IX, 1950.

Since 1948 all articles appearing in the *Annals of the Rheumatic Diseases* have had summaries translated into French. In view of the increasing circulation in South America it has been decided to include Spanish summaries as well, and these will begin with the first issue of 1950.

MUSCLE LESIONS IN RHEUMATOID ARTHRITIS*

BY

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Recently certain pathological investigations have indicated that there is frequently widespread involvement of the neuromuscular system in rheumatoid arthritis, and it has been suggested that this may be responsible for the prominent neuromuscular clinical features of the disease.

Curtis and Pollard (1940) were the first to describe the non-articular lesion which was common to all their eleven cases of rheumatoid arthritis, including four cases with " Felty's Syndrome ". In every one of their eleven cases these authors found small perivascular infiltrations of lymphocytes in the muscles.

Steiner and others (1946) performed muscle biopsies on seven cases of rheumatoid arthritis and demonstrated inflammatory nodules in each of the cases. The nodules were situated in the perimysium and in the endomysium, rarely in the epimysium. The nodules consisted of collections of lymphocytes and plasma cells and the authors termed the lesion " nodular polymyositis ". Similar lesions were encountered in the muscles of two cases which were examined at autopsy. The size of the nodules varied from very small ones (consisting of " twenty or less lymphocytes ") to large ones visible to the naked eye in the stained sections. They also noted definite arteritis and peri-arteritis in the small muscular vessels in some of their cases. In addition to the nodular inflammatory lesions they noted the occurrence of various stages of degeneration and atrophy of the muscle fibres and considered that these degenerative changes, when present, were always secondary to the inflammatory changes. The lesions were found in muscles which were not adjacent to affected joints, and were present even in long-standing cases of rheumatoid arthritis which were " seemingly burnt-out ". They suggested that these findings were specific to rheumatoid arthritis.

These results were soon confirmed by other investigators. Gibson and others (1946) noted the presence of these nodular inflammatory lesions by biopsy in each of eleven cases of rheumatoid arthritis. De Forest and others (1947) found similar characteristic lesions in twelve out of sixteen muscle biopsies. Clawson and others (1947) demonstrated these characteristic lesions in seventeen out of forty-four deltoid muscle biopsies. Desmarais and others (1948) reported the results of muscle biopsies on a further fifty-six cases of typical idiopathic rheumatoid arthritis. Thirty-four of these cases showed round-cell foci and blood-vessel changes. Like Steiner and others, they noted " positive " biopsies in cases which appeared " burnt-out ", in cases without muscle wasting, and in muscles remote from affected joints. Bunim and others (1948) stated that they found the characteristic small nodules in the " large majority " of the muscle biopsies performed on twenty-five cases of typical rheumatoid arthritis.

It thus appears, when these results are analysed, that " positive " muscle biopsies (with " nodular myositis ") occurred in 40 to 100 per cent. of cases of rheumatoid arthritis. If the results are totalled it appears that, on the average, approximately 60 per cent. of muscle biopsies in rheumatoid arthritis reveal the characteristic lesions described by Steiner and others (1946).

Morrison and others (1947) examined the muscles of fourteen cases of rheumatoid arthritis at autopsy and encountered varying sizes of inflammatory nodules in eight instances.

Results of Muscle Biopsy in Thirty-four Cases of Rheumatoid Arthritis

Muscle biopsy was performed under local anaesthesia with 2 per cent. procaine on thirty-four cases of chronic rheumatoid arthritis. The deltoid muscle was selected in thirty-three cases and the gastrocnemius in one case. The cases were typical examples of " idiopathic " chronic rheumatoid arthritis, the durations varying from one year to forty-five years. The size of an average piece of muscle removed by biopsy was approximately 1·8 cm. in length, 0·6 cm. in breadth, and 0·6 cm. in

* Extracted from a thesis accepted for the degree of M.D., University of Cape Town.

thickness. The biopsy specimens were fixed in corrosive sublimate and embedded in paraffin wax. Three sections were cut from each specimen and were stained with haematoxylin and eosin.

Attention was chiefly focused on the inflammatory changes in the muscles. It was sometimes difficult to distinguish with certainty between degenerative changes in the muscles and changes resulting from the trauma of removal. As the inflammatory changes, not the degenerative ones, are those which have been regarded as probably of diagnostic value in the disease, the degenerative changes are mentioned more briefly.

Characteristic inflammatory lesions were found in fourteen cases (40 per cent.) in the series. The muscle biopsies were " negative " in the remaining twenty cases.

A single focus was present in six cases; two to seven foci were found in the other eight cases.

The Fourteen " Positive " Biopsies

The results of the microscopic examinations of the sections of the fourteen " positive " biopsies are tabulated and illustrated below.

Case 1.—A 51-year-old man had rheumatoid arthritis for three years. Two large oval nodules consisting of about 100 cells each and one small nodule consisting of about 40 cells were present in the endomysium and were perivascular in distribution. The cells were practically all lymphocytes.

Case 2.—A 60-year-old woman had rheumatoid arthritis for seven years. One small nodule consisting of about fifty lymphocytes was situated in the endomysium on the edge of the section.

Case 3.—A 61-year-old woman had rheumatoid arthritis for twenty years. One nodule consisting of about fifty small round cells (chiefly lymphocytes with a few plasma cells) was found in the perimysium.

Case 4.—A 66-year-old woman had rheumatoid arthritis for five years. Very extensive lesions were present in the muscle. Three tiny blue foci were visible in the section on naked-eye examination, varying in size from a pin-point to a pin-head. Microscopically, four smaller foci could also be detected. The nodules consisted of small round-cells, chiefly lymphocytes with a few plasma cells, but in one focus plasma cells were the prominent cells. Scanty eosinophils were present in the nodules. The shape of the nodules varied: some were oval, others elongated, and several were fusiform. One nodule was very large and replaced a large area of muscle (Fig. 1). It was situated in the endomysium, and collections of cells straggled out from the main nodule between the adjacent muscle fibres. A few small portions of muscle fibre were isolated in the centre of this large nodule. A second nodule was about half the size of this large nodule, while an oval-shaped third nodule (Fig. 2) was about one-third the size of the large nodule. This latter nodule was closely related to a few small blood vessels (Fig. 2). The remaining smaller nodules each consisting of about 100 cells were present in the endomysium and were perivascular in distribution. The blood vessel was usually situated near the end of the nodule, not in its centre.

Case 5.—A 40-year-old woman had rheumatoid arthritis for five years. Extensive lesions were present but not to quite the same degree as in Case 4. Four of the five nodules present could be identified in the sections with the naked eye. The nodules were situated in the endomysium. Only one of the five nodules was perivascular in distribution; the others were not related to any blood vessels. They were chiefly spindle-shaped (Fig. 3). In one area the cells could be seen surrounding the muscle fibres in transverse section (Fig. 4). The size of the nodules varied. The smallest nodule consisted of about a hundred cells, while the largest contained several hundred. Lymphocytes comprised the vast majority of the cells in each case. The muscle fibres often showed fragmentation at the sites of the muscular infiltration.

Case 6.—A 35-year-old man had rheumatoid arthritis for eight years. One irregularly-shaped perivascular nodule consisting of about seventy-five lymphocytes was present in the perimysium.

Case 7.—A 39-year-old woman had rheumatoid arthritis for six years. Two small nodules, each consisting of about forty-five small round-cells, were situated in the endomysium.

Case 8.—A 57-year-old woman had rheumatoid arthritis for eight years. Six small nodules, each consisting of about forty to sixty small round cells, were present in the endomysium. The nodules were perivascular in three instances.

Case 9.—A 44-year-old man had rheumatoid arthritis for twelve years. Two large triangular perivascular nodules, each consisting of about two hundred cells, were present in the perimysium. The cells were chiefly lymphocytes, but a few plasma cells were also present. An occasional arteriole in other parts of the section showed some slight perivascular infiltration with about ten to fifteen lymphocytes, and scanty round-cell infiltration was present between some muscle fibres.

Case 10.—A 39-year-old man had rheumatoid arthritis for two years. Six small nodules, consisting of thirty to forty small round cells, were distributed perivascularly in the endomysium and in the perimysium.

Case 11.—A 47-year-old woman had rheumatoid arthritis for one year. One perivascular nodule consisting of eighty small round cells and three smaller nodules, each consisting of thirty to forty cells were found.

Case 12.—A 46-year-old man had rheumatoid arthritis for eight years. One paravascular spindle-shaped nodule consisting of about eighty lymphocytes was present in the endomysium.

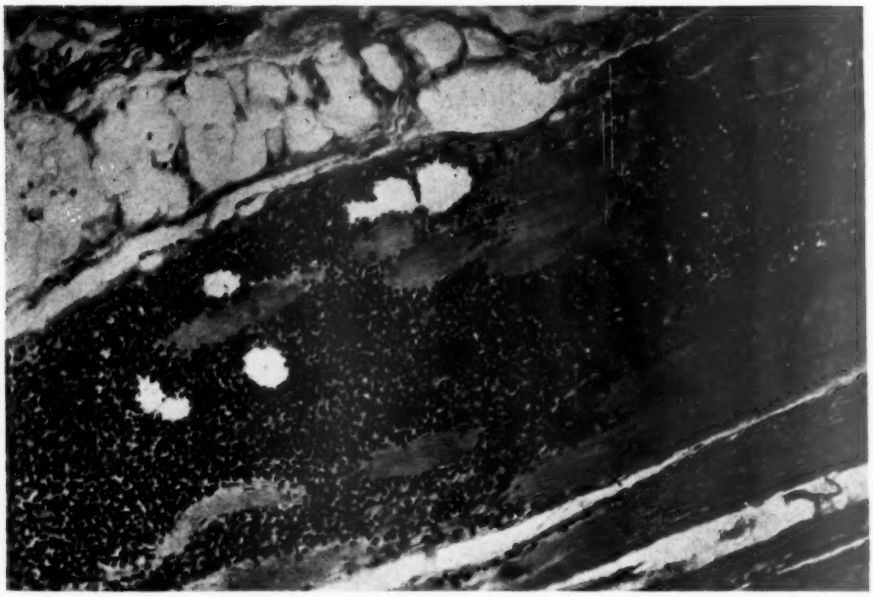

FIG. 1.—Case 4. Very large inflammatory nodule, consisting chiefly of lymphocytes. It is situated in the endomysium, and linear collections of cells extend between adjacent muscle fibres. A large part of the muscle is replaced by the " nodular myositis ". (Haematoxylin and eosin, × 130.)

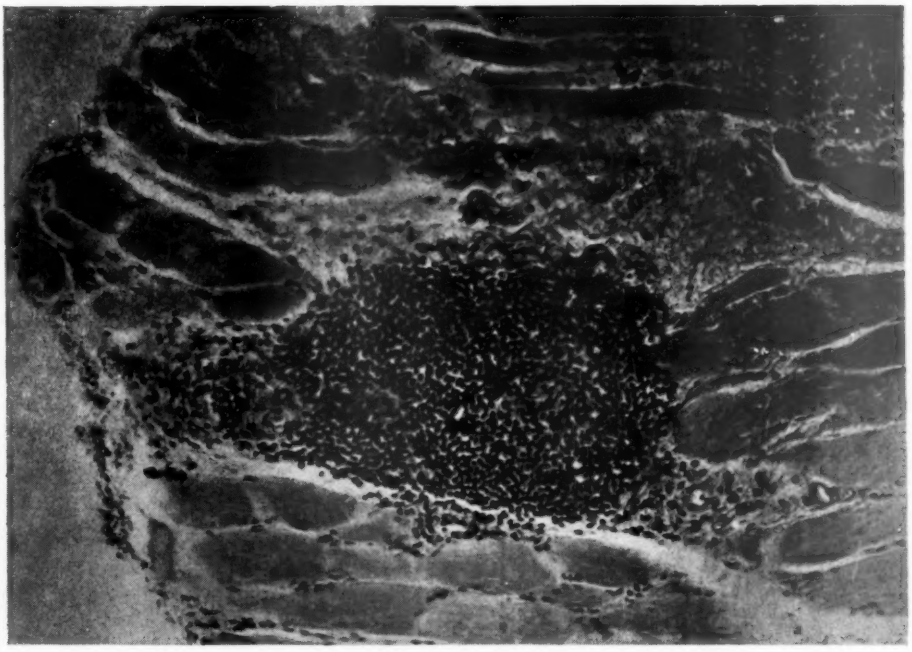

FIG. 2.—Case 4. A large focus consisting of small round cells replaces part of the muscle. Small blood-vessels are present at one edge of the focus. (Haematoxylin and eosin, × 130.)

FIG. 3.—Case 5. Spindle-shaped focus of lymphocytes in endomysium. (Haematoxylin and eosin, × 130.)

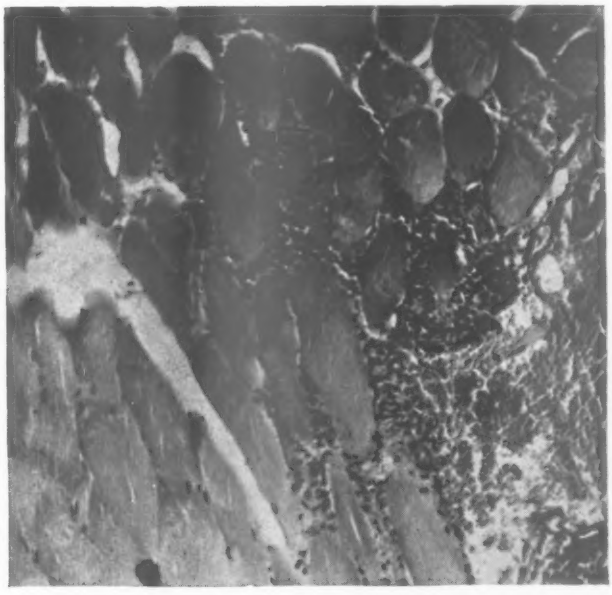

FIG. 4.—Case 5. Collections of lymphocytes seen encircling muscle fibres in transverse section. (Haematoxylin and eosin, × 130.)

Case 13.—A 60-year-old woman had rheumatoid arthritis for one year. A small irregularly-shaped collection of about forty small round cells was seen encircling a muscle fibre.

Case 14.—A 70-year-old woman had rheumatoid arthritis for four years. One small paravascular nodule consisting of about forty-five small round cells was present in the perimysium.

Discussion

The results of the deltoid muscle biopsies were " positive " in approximately 40 per cent. of the thirty-four cases examined. These findings thus confirm the reported incidence of the inflammatory foci and nodules in the muscle in rheumatoid arthritis. The incidence encountered in this series is lower than that noted by most of the investigators, but corresponds closely to the results recorded by Clawson and others (1947) in their forty-four biopsies.

A striking feature was the ease with which the inflammatory nodules could be recognized and identified. They appeared in sharp contrast to the surrounding muscle fibres, and could be easily detected. In two instances (Case 4, Figs. 1 and 2 ; and Case 5), the nodules were sufficiently large to be visible in the stained sections on naked-eye examination.

The nodules varied in size from small foci consisting of approximately thirty small round cells to very large nodules visible macroscopically. Fig. 2 illustrates the appearance of such a very large nodule, whilst Fig. 4 illustrates a smaller collection of cells. The shape of the nodules varied. Some were round, others triangular, others oval, others elongated, and others spindle-shaped. The edges sometimes " tailed off " between adjacent muscle fibres (Fig. 1). The nodules were encountered in the endomysium and in the perimysium. They were often perivascular or paravascular in situation, but some nodules occurred without any obvious relation to a blood vessel.

The cells consisted mainly of lymphocytes, with a variable number of plasma cells and a few eosinophils in some nodules. The muscle fibres at the edges of the larger nodules often showed atrophy and fragmentation. In some nodules muscular remnants could still be recognized. However, there was no close parallelism between the degree of inflammatory change and the degree of muscular atrophy.

There was no close relationship between the finding of " positive " muscle biopsy and the degree of " activity " of the arthritis. Case 9, for example, was clinically " burnt-out ", and had a normal sedimentation rate, yet two large inflammatory nodules were seen in the muscle biopsy sections. There were no clinical differences noted between these cases with " positive " biopsies and those cases with " negative " biopsies.

The conclusion therefore appears to be that one nodule or multiple nodules are commonly found in sections of muscle removed by biopsy in cases of rheumatoid arthritis. The results are all the more striking as only small portions of muscle were removed at biopsy and yet the lesions were readily detected in fourteen of the thirty-four cases examined (40 per cent.). The histological findings in this series of fourteen " positive " biopsies conform to the descriptions of " nodular polymyositis " given by Steiner and others (1946).

However, it must be realized that the results of the reported investigations and of the present investigation have confirmed only one point, that is, the high incidence of " nodular myositis " in cases of rheumatoid arthritis. The other problem, which was immediately presented to Steiner and others (1946) and to other workers, was whether these findings are specific to rheumatoid arthritis or whether they also occur in a variety of conditions. Neurologists, for example, have often described the occurrence of " lymphorrhages " in the muscles of cases of myasthenia gravis (Kinnear Wilson, 1940 ; Russell Brain, 1947), yet this fact appears to have been largely overlooked by various investigators.

Review of the Literature on Control Cases

Steiner and others (1946) examined muscles in a series of controls from 196 routine autopsies. With the exception of one case of dermatomyositis and one case of trichiniasis, they were unable to demonstrate " nodular myositis " in any of these muscles.

Morrison and others (1947) examined a control series of muscles in fifty autopsies ; in a " few cases " of dermatomyositis, disseminated lupus erythematosis, and scleroderma, they found muscle lesions which closely resembled the inflammatory nodules in rheumatoid arthritis, but the rest of the controls were " negative ".

De Forest and others (1947) performed muscle biopsies on ten control cases (excluding the four cases of " non-specific infectious arthritis ", and their one case of osteo-arthritis which " had a history suggestive of rheumatoid arthritis ") and were unable to find any instances of " nodular myositis " in these ten cases.

Desmarais and others (1948), in their series of control muscle biopsies, found characteristic foci of

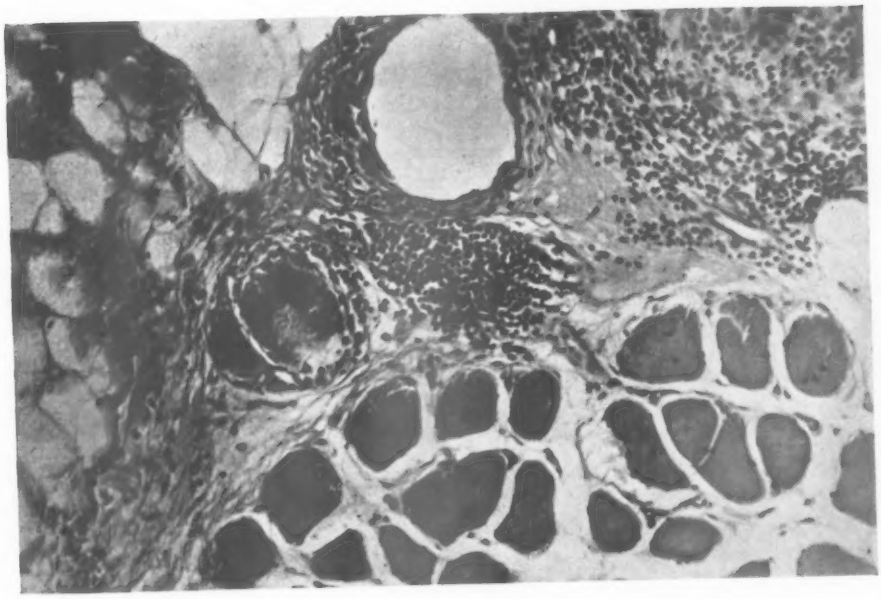

FIG. 5.

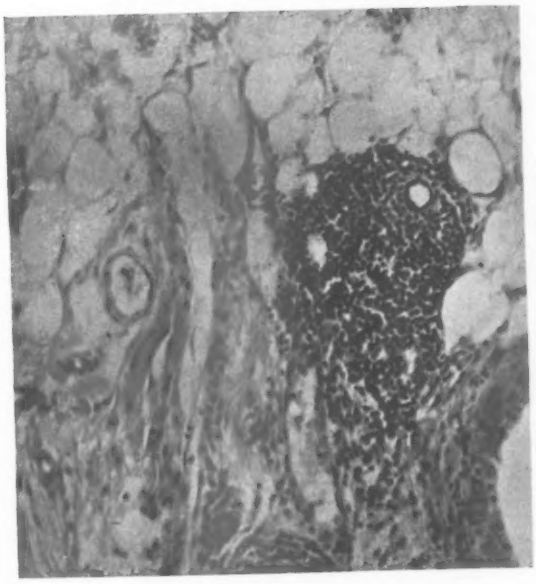

FIG. 6.

FIGS. 5 and 6.—*Gout.* Inflammatory foci, consisting chiefly of lymphocytes, were noted in the sections from a deltoid muscle biopsy in a case of gout. The foci resembled those seen in rheumatoid arthritis, but differed in being accompanied by several "foreign-body" giant cells (as in tophi), and by being situated mainly in the subcutaneous tissue, extending into the epimysium. (Haematoxylin and eosin, × 130.)

" nodular myositis " in one case of Still's disease, but the remainder of their controls were " negative " (including four cases of subacute rheumatic infection with cardiac involvement ; one case of rheumatic fever with rheumatic heart disease ; seventeen cases of ankylosing spondylitis ; six cases of gout ; six cases of osteo-arthritis ; three cases of polio-myelitis ; three cases of specific infective arthritis ; one case of Paget's disease ; one case of prolapsed disc ; and one case of amyotonia congenita). One case of Volkmann's ischaemic contracture showed diffuse round-cell infiltration in the fibrous tissue among the muscle fibres, but the cells were not related to blood vessels as in rheumatoid arthritis. Two cases of reaction to muscle trauma had lesions similar to " nodular myositis ". One case of tuberculous spondylitis had a tiny paravascular focus consisting of about twenty lymphocytes. Thus, with rare exceptions (chiefly in post-traumatic cases) their control series did not reveal lesions of " nodular myositis ", and this finding, in their opinion, emphasized the importance of its high incidence in rheumatoid arthritis.

The finding of muscle lesions in such conditions as dermatomyositis, disseminated lupus erythematosus, and scleroderma, indicated that nodules of inflammatory cells in muscles could not be regarded as quite specific to rheumatoid arthritis. These observations do not greatly detract from the value of muscle biopsy in rheumatoid arthritis, as the diseases mentioned above are comparatively rare, and as there might be some as yet undetermined relationship between them and rheumatoid arthritis.

However, Clawson and others (1947) have reported results which, if correct, are irreconcilable with the findings of all the previous investigators. They collected seven muscles from each of 450 autopsies, and in 118 cases (that is 26 per cent.) inflammatory lesions were observed in one or more muscles and of one or more grades ! They divided their inflammatory lesions into four grades : their grade 4 corresponds with one of the large nodules illustrated by Steiner and others, and their grade 1 resembles a small nodule as illustrated by Steiner and others (1946). They noted these " positive " biopsy results in a wide variety of diseases : acute rheumatic fever, bacterial endocarditis, hypertension, coronary sclerosis, accidents and trauma, " tumors ", cerebral haemorrhage, cirrhosis, " gastro-intestinal conditions ", tuberculosis, poliomyelitis, pneumonia, infections of the bladder and kidneys, etc.

These results, if correct, challenge the validity of the results reported by Steiner and others (1946), Desmarais and others (1948), de Forest and others (1947), and Morrison and others (1947) in their series of control cases.

It is difficult to find a possible source of error in Clawson and others' investigations (1947). They admitted that " rheumatoid arthritis may have been present to some extent without being mentioned in the histories " in some of their cases, but statistically it is very improbable that coincidental rheumatoid arthritis was present in more than a fraction of the cases.

Nor can it be said that the criteria employed by Clawson and others (1947) in their diagnosis of " positives " were very different from those employed by former workers. They specifically stated that they did not regard " the presence of but a few lymphocytes " as indicating a " positive result ". Their illustrations of " positive results " appear similar to those shown by previous investigators. Most of their " positive " results were grouped in grades 1 and 2, but many were grouped in grades 3 and 4, and were thus examples of large nodules. Clawson and others commented that the lesions were found more frequently in cases in which death occurred in the upper decades of life.

Yet in an extensive examination of muscles in " control " cases (including approximately sixty muscle biopsies, and the examination of muscles of approximately 250 cases at autopsy), Steiner and others (1946), de Forest and others (1947), Morrison and others (1947), and Desmarais and others (1948) noted no " positive " results with the exception of the few cases of dermatomyositis, etc., mentioned above.

Bunim and others (1948) also stated that the characteristic muscular nodules were present in many diseases in their control group. The histological appearances and anatomic locations of these nodules were strikingly similar to, and in some cases indistinguishable from, those seen in rheumatoid arthritis. Their control series included not only cases of rheumatic fever, Still's disease, ankylosing spondylitis, lupus erythematosis, and dermatomyositis, but also cases of gout, osteo-arthritis, gonococcal arthritis, tuberculous arthritis, and Pott's disease. Bunim and others therefore concluded that if the nodules occurred in a number of unrelated diseases then they could hardly be considered to be specific for rheumatoid arthritis. Bennett (1948) agreed with these conclusions, although his " observations were limited ".

On the other hand, Freund (1948) has repeated his belief that the nodules of " nodular myositis " are specific for rheumatoid arthritis. He agreed that similar nodules may occur in disseminated

lupus erythematosus, in dermatomyositis, in trichiniasis, and in Still's disease, but denied that the nodules occurred in other conditions such as ankylosing spondylitis, gout, osteo-arthritis, and gonococcal arthritis.

How are these diverse results to be reconciled? It is possible that Clawson and others (1947) detected the high incidence of muscle lesions in numerous diseases on account of their extensive examinations on seven muscles at each of the 450 autopsies, whereas the other observers have examined only smaller pieces of muscle removed by biopsy or at autopsy. Nevertheless, if Clawson and others (1947) and Bunim and others (1948) are correct in their observations, then these observations constitute a very serious obstacle to the claims that these inflammatory nodular foci found in muscle in cases of rheumatoid arthritis are in any way diagnostic of the disease.

Results of Muscle Examination in Twenty Control Cases

Muscle biopsies were performed in twelve control cases. The muscle was obtained from the deltoid in nine cases (consisting of two cases of acute rheumatic fever, one case of osteo-arthritis, one case of "fibrositis", one case of generalized scleroderma, one case of acute diffuse glomerulonephritis, two cases of gout, and one case of acute poly-arthritis of unknown aetiology); from the pectoral muscle of a case of hypertension; and from the sacrospinalis and gastrocnemius muscles respectively in two cases of polyarteritis nodosa.

In addition, muscle was examined at autopsy in eight cases. The gastrocnemius was examined in a case of acute porphyria, and the deltoid was examined in the other seven cases (consisting of two cases of miliary tuberculosis; one case of generalized peritonitis; one case of myocardial infarction; and three cases of death due to violence).

Although the series of control cases is admittedly small, it is interesting that (with three exceptions) no muscle lesions were encountered in the twelve muscles examined by biopsy and in the eight muscles examined at autopsy.

Of the three cases with muscular lesions, two were cases of polyarteritis nodosa in which the expected characteristic vascular lesions were found (Selzer and Horwitz, 1949). They were distinguishable from the lesions of "nodular myositis" in the rheumatoid arthritis series.

The third case with muscular lesions had gout (the diagnosis had been proved by demonstrating the presence of sodium biurate crystals in a tophus removed from the elbow (Horwitz, 1949)). The deltoid muscle biopsy was performed while the patient was suffering from an attack of gout in the knees and ankles. The histological appearances were interesting (Figs. 5 and 6), and have not been noted hitherto in examinations of muscle biopsies. Inflammatory foci were present which closely resembled those seen in rheumatoid arthritis, but it was at once possible to differentiate sections from those of the rheumatoid arthritis series by means of two features: (1) Numerous foreign-body giant cells were present in, or at the edge of, several of the inflammatory foci (Fig. 5). The lesions thus seemed to resemble those seen in tophi and were presumably a tissue reaction to the local deposition of biurate crystals. (2) The majority of the inflammatory foci were situated in the connective tissue on the surface of the deltoid muscle (Fig. 6), extending into the epimysium and sometimes into the perimysium. The situation of the inflammatory foci was thus primarily in the subcutaneous tissue, and the extension into the muscle appeared to be secondary. A deltoid muscle biopsy was performed on a second case of gout, but no lesions were found in the connective tissue or in the muscle. The "positive" result in the first case of gout is interesting as it probably indicates a deposition (in the past attacks or in the present attack of gout) of sodium biurate in the deep subcutaneous tissue, and in the intramuscular connective tissue. It is well known that tophi may occur, not only in joints, cartilage, bursae, and tendons, but also in subcutaneous tissue, and the histological appearances in this case probably represent "a microscopic tophus". (No tophi were present over the shoulders on clinical examination before the muscle biopsy was performed).

Summary

1. In a series of muscle biopsies performed in thirty-four cases of rheumatoid arthritis, nodules were found in the endomysium or in the perimysium in fourteen cases. The histological appearances closely resembled the descriptions of "nodular myositis" in the literature. The findings confirmed the fairly high incidence of these muscle lesions in rheumatoid arthritis.

2. The lesions were noted in "active" and in "burnt-out" cases.

3. The nodules were detected with great facility on histological examination. In some cases they were sufficiently large to be visible to the naked eye.

4. In an examination of the muscles of a small control series of twenty cases, by biopsy or at autopsy, similar inflammatory nodules were found in only one case—a case of gout. Certain additional features rendered the differentiation possible from

the "nodular myositis" seen in rheumatoid arthritis. Two cases of polyarteritis nodosa showed the characteristic vascular lesions of that disease.

Muscle examinations in two cases of polyarteritis nodosa showed the characteristic vascular lesions encountered in the disease.

5. In reviewing the literature it was noted that some investigators have reported the occurrence of "nodular myositis" in a miscellaneous collection of diseases. If their findings are confirmed, it would indicate that "nodular myositis" is a comparatively common condition in a wide variety of diseases and that it is of no diagnostic value in cases of rheumatoid arthritis.

The number of control cases in this series was too small to enable final conclusions to be drawn, but the results were more in conformity with the "negative" findings noted by most investigators in the examination of muscle in control cases.

I am greatly indebted to Prof. F. Forman, Dr. P. W. J. Keet, and the Hon. Physicians of the Groote Schuur Hospital, Cape Town, for permission to investigate the cases under their care; to Prof. B. J. Ryrie and Prof. M. van den Ende for assistance and facilities afforded in the Department of Pathology, University of Cape Town; to Dr. G. Selzer for valuable assistance in the histological examinations; to Mr. W. Taylor for the histological preparations; and to Mr. G. C. McManus for the microphotography. A grant from the Staff Research Fund, University of Cape Town, is gratefully acknowledged.

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Lésions Musculaires dans la Polyarthrite Chronique Inflammatoire

Résumé

1. Une série de biopsies musculaires pratiquées dans trente-quatre cas de polyarthrite chronique inflammatoire, a montré, dans quatorze cas, des nodules dans l'endomysium et le perimysium. L'aspect histologique ressemblait beaucoup à ce qu'on décrit sous le nom de "myosite nodulaire" dans la littérature. Les constatations confirmèrent l'assez grande fréquence de ces lésions musculaires dans la polyarthrite chronique inflammatoire.

2. On remarqua ces lésions dans des cas qui étaient en phase évolutive ou en phase de "calme".

3. Les nodules furent découverts très facilement à l'examen histologique. Dans certains cas, ils étaient assez importants pour être vus à l'oeil nu.

4. Pour une série de vingt "cas témoins" (2 rhumatismes articulaires aigus, 1 ostéoarthrite, 1 cellulite, 1 sclérodermie, 1 glomérulo-néphrite aigüe, 2 gouttes, 1 polyarthrite d'étiologie inconnue, 1 hypertension, 2 périartérites noueuses, 1 porphyrinurie aigüe, 2 tuberculoses miliaires, 1 péritonite généralisée, 1 infarctus du myocarde, 3 cas de mort violente), l'examen des muscles, par biopsie ou à l'autopsie, ne révéla la présence de semblables nodules inflammatoires que dans un seul cas, un cas de goutte. Certaines différences d'aspect permirent le diagnostic avec la "myosite nodulaire" caractéristique de la polyarthrite chronique inflammatoire.

L'examen musculaire de deux cas de périartérite noueuse mirent en évidence les lésions vasculaires caractéristiques rencontrées dans cette maladie.

5. On remarque dans la littérature que certains auteurs ont signalé la présence de "myosite nodulaire" dans une série de maladies diverses. Si leurs constatations sont confirmées, cela semblerait prouver que la "myosite nodulaire" est rencontrée assez communément dans une grande variété de maladies et qu'elle n'a pas de valeur diagnostique dans les cas de polyarthrite chronique inflammatoire.

Dans cette série le nombre des "cas témoins" fut trop faible pour permettre d'en tirer des conclusions définitives, mais les résultats semblent plutôt confirmer l'opinion de la plupart des auteurs à savoir l'absence habituelle des nodules typiques de la polyarthrite chronique inflammatoire en dehors de cette maladie.

MORQUIO-BRAILSFORD'S DISEASE SIMULATING THE ARTHRITIC MANIFESTATION OF RHEUMATOID DISEASE

BY

PHILIP ELLMAN

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Rheumatoid disease in its acute or chronic form with its systemic or local manifestations may at one time or another simulate many diseases. Its local joint manifestations may resemble many specific arthritides and bony lesions with secondary joint involvement (Ellman and Ball, 1948). The purpose of this paper is to give an account of two cases of a chondro-osseous dystrophy, one of which, and possibly also the other, had at first been regarded as due to an arthritic manifestation of "rheumatoid disease". This disorder was first described by Morquio in 1929, when he reported two cases in a family of five affected children. In the same year Brailsford (1929) independently described his first case. The condition is now often referred to as the Morquio-Brailsford type of chondro-osseous dystrophy.

The primary disorder is an abnormality of development of the skeletal tissues which may vary in severity from changes apparently incompatible with life, to mild deformities of the trunk or limbs. It is characterized by multiple irregular centres of ossification in the epiphyses and diaphyses, followed later by superimposed secondary deformities and also marked muscle weakness, but even more characteristic are the constant changes in the spine—the shallow flattened vertebra with, in typical cases, the characteristic shape in the lateral view of the central tongue projecting (Figs. 6, 7, 15, 16). Of the epiphyses the hips are the most frequently affected, and in the majority of cases they show a large irregular acetabulum (Figs. 8, 10, 17), but the other epiphyses are much less often affected to any obvious degree. The reported cases have been divided by Brailsford into four separate groups.

Briefly, Group A is the most severe form, in which the spine and hip joints are mainly affected. The epiphyses of the long bones are much larger and the shafts shorter and thicker than normal. The feet and hands are also deformed, but the skull remains unaffected. With an associated muscle weakness, cases in this group run a progressively downhill course.

Group B is a variation of Group A in that the same joints are affected but the active phase seems to exhaust itself by the time puberty is reached, leaving crippling malformations.

In Group C the disorder is confined to the spine and hip joints, although the knees are occasionally affected.

In Group D only the vertebral column is affected.

The dwarfing which characterizes many cases is due in the main to spinal changes. The condition of the spine and hips are the two diagnostic features. Where the epiphyseal changes are marked, the differential diagnosis from dysplasia epiphysealis multiplex must be considered (Fairbank, 1947).

Case Histories

Case 1.—This case has previously been described (Ellman, 1933) and has been closely followed up for a further seventeen years. The striking feature of the case has been the patient's determination throughout to overcome his disability despite his gross skeletal deformity; through home education he has managed at intervals of time during this period to take matriculation and the degrees of B.Sc. and Ph.D., and he is now a medical student since he feels that his vocation, biochemistry, cannot adequately be mastered without a full medical training.

This patient was first seen as a boy of 15 years. He had been "healthy" till the age of 4 years, when he had an attack of measles, after which he was easily fatigued and complained of increasing stiffness, joint swellings, and inability to walk. As he became older the swellings became progressively worse.

He was an only son of parents who were first cousins. There is no family history of deformities on either side.

On examination he was found to be 4 ft. 4 in. high (normal 5 ft. 5 in.) and to weigh 5 st. 7½ lb. There was great distortion of the trunk and extremities. The trunk was very short and there was a marked kyphosis and

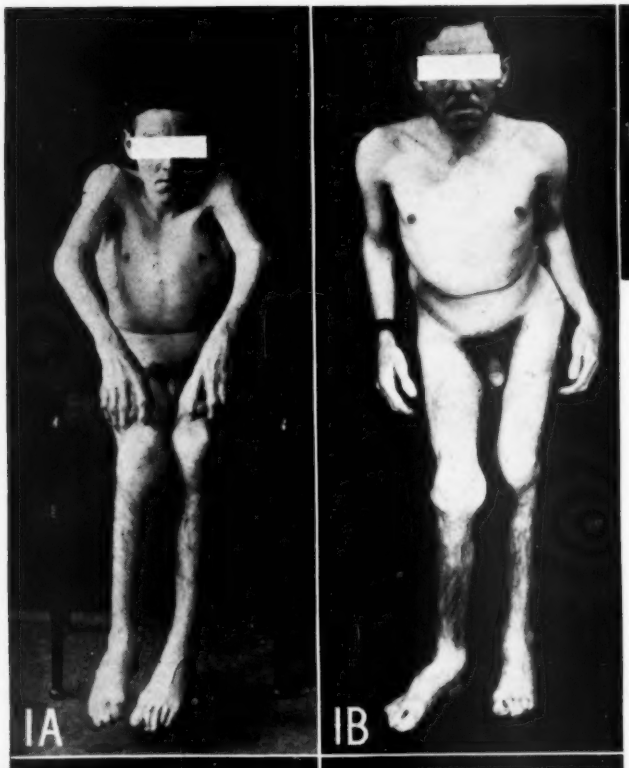


FIG. 1.—Anterior views of Case 1, (a) 1933 and (b) 1949.

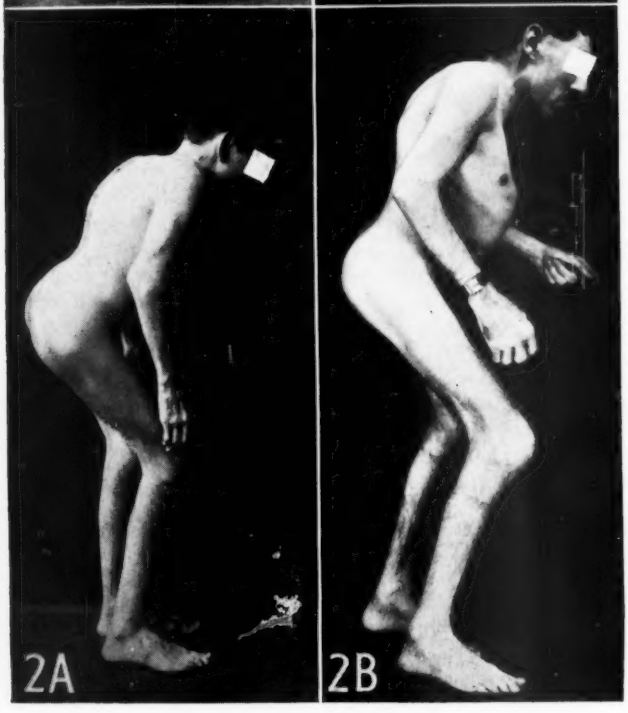
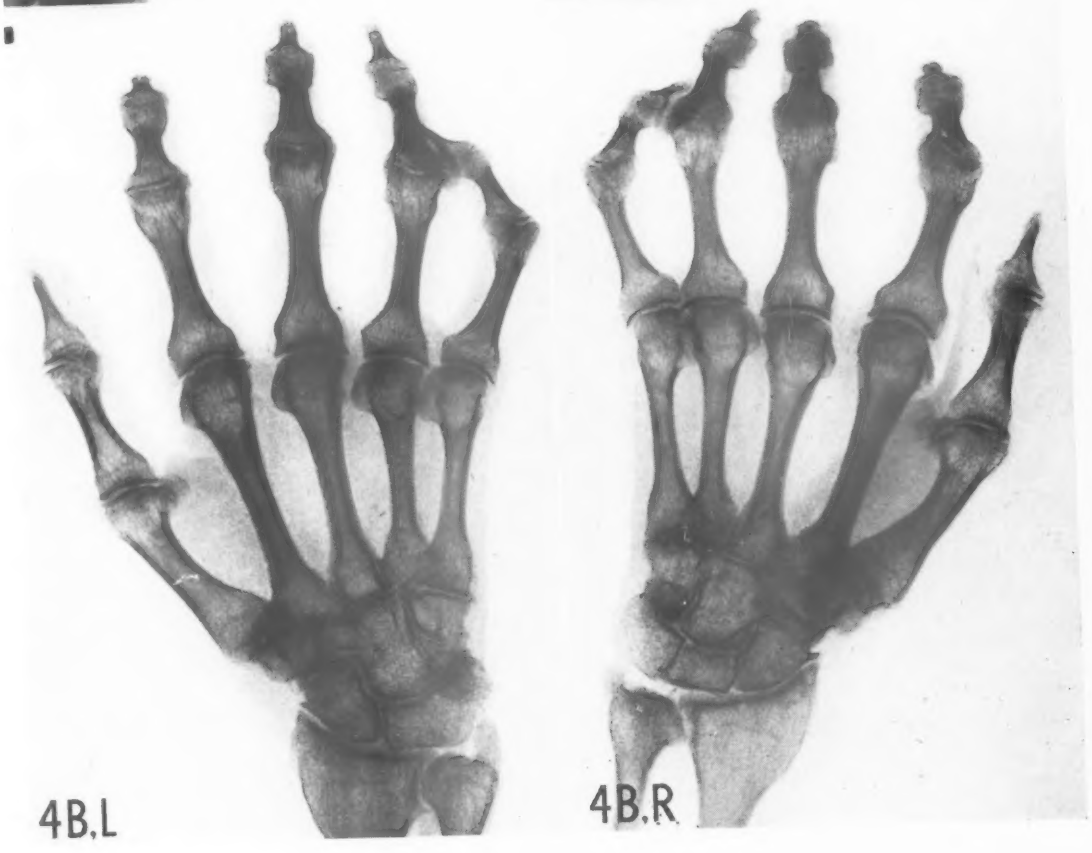
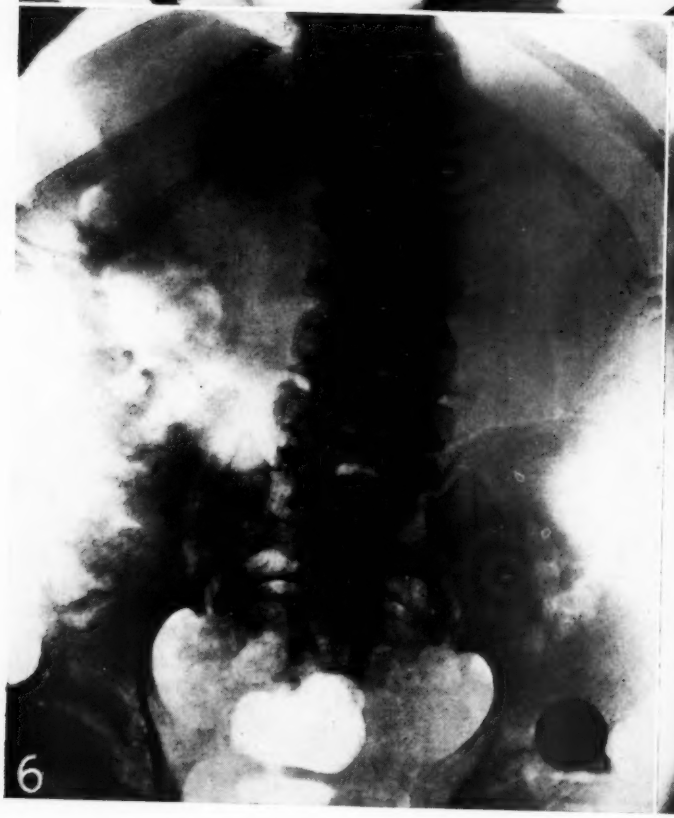


FIG. 2.—Lateral views of Case 1, (a) 1933 and (b) 1949.

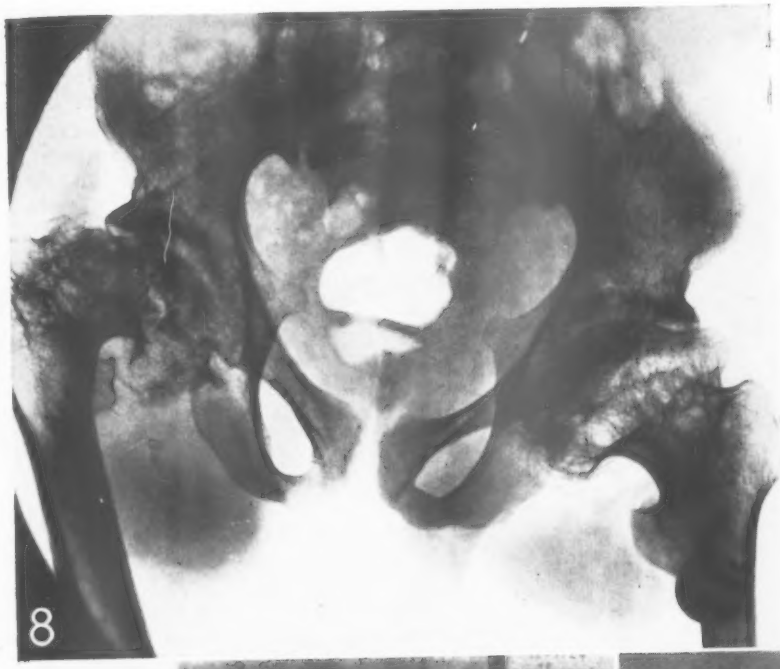
FIG. 3.—Hands of Case 1, 1949.

FIG. 4.—Radiographs of hands, Case 1.

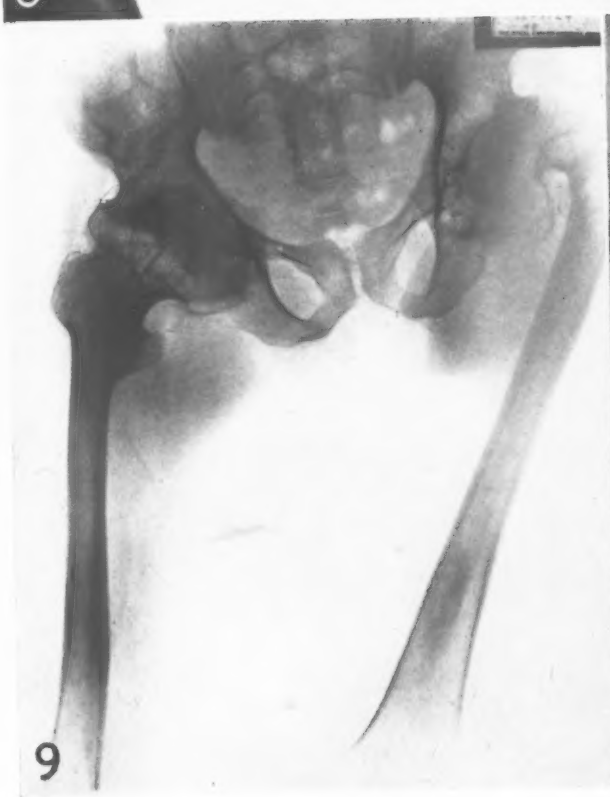


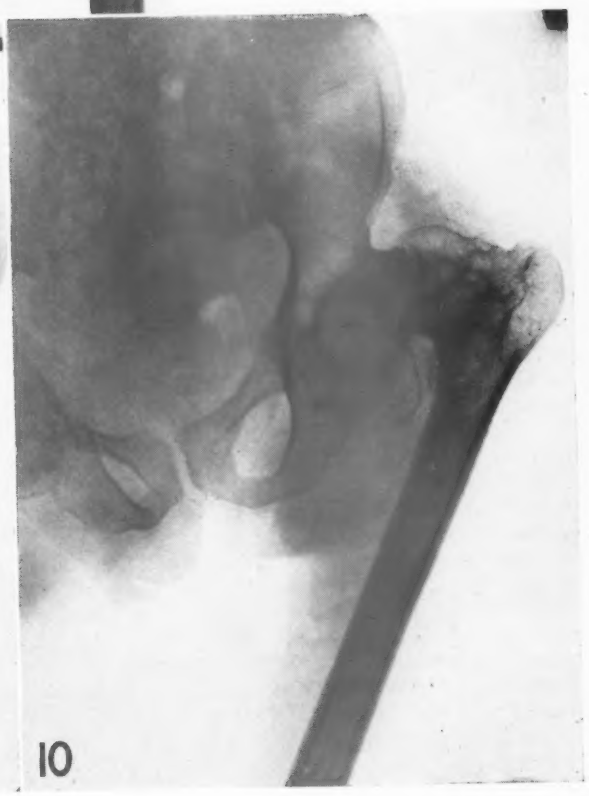


FIGS. 5-7.—Radiographs of Case 1.



FIGS. 8-10.—Radiographs of Case 1.





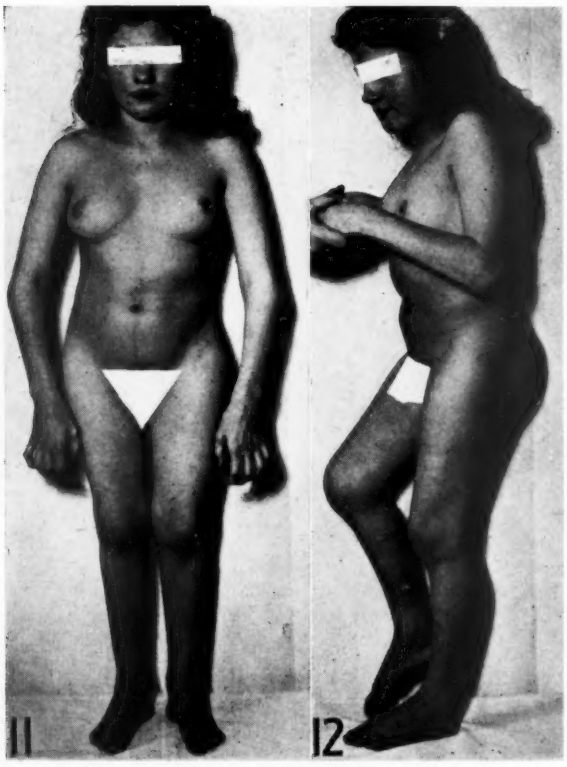


FIG. 11.—Case 2, showing disproportion.

FIG. 12.—Lateral view of Case 2, showing maximum flexion of the right hip.

pigeon-breast deformity. The normal standing position was one of crouching with the pelvis tilted forwards and to the left. The head is normal and the face is intelligent.

There was marked swelling and limitation of movement of almost all the joints, and considerable generalized muscular wasting (Figs. 1, 2, 3). There were no abnormalities in the cardiovascular, respiratory, central nervous, gastro-intestinal, or genito-urinary systems.

X-ray examination of the locomotor system has revealed the following abnormalities. All the bones show marked evidence of osteoporosis. The shafts of the long bones are attenuated, and the epiphyseal ends are enlarged. The heads of the femora are considerably distorted, and there is marked irregularity of the articular cartilage. There is distortion of the lower ends of the femora and upper ends of the tibia, and well marked expansion of the ends of the phalanges and metacarpal bones, with slight attenuation of the shafts of the bones. There is apparent destruction of the terminal phalangeal joints (Figs. 4-10).

Case 2.—A girl, aged 16 years, was referred to me by Dr. William Mackenzie of the W. J. Sanderson Orthopaedic Hospital School for Children, Newcastle, through the courtesy of Sir Thomas Fairbank. She was "healthy" until the age of 6 years, when painless swellings of her fingers were first noticed, which became progressively worse for two years and have since remained in the same condition. At the age of 10 years difficulty in walking was noticed, and this also became progressively worse so that for a period she was unable to walk. She lived at an Orthopaedic School for four years, and during that time learnt how to walk again. Her mental development is normal for a person of her age, and periods began at the age of 13 years. She was admitted to the Rheumatism Unit at St. Stephen's Hospital under my care (Figs. 11, 12).

The girl is the fifth child of her mother, who in the second marriage married her first cousin. Two are children of the first marriage and there are four children of the second marriage. All these are normal except the patient and one son, aged 26 years, who is only 5 ft. tall but exhibits no disproportion or radiological evidence of abnormality. The mother is also only 5 ft. tall, but exhibits no abnormality comparable to that of her daughter.

As the other members of the family were so short, the patient's small stature passed unnoticed for many years.

On examination she was found to be 4 ft. 3 in. high and to weigh 5 st. 8 lb. Her legs and arms were disproportionately long for her trunk ; her head was normal but set on a very short neck. There was marked dorsal kyphosis, and the chest had an increased antero-posterior diameter. The epiphyses of all the long bones especially the elbows and knees, were enlarged. The hands showed swellings and flexion deformities of all the interphalangeal joints and the lack of wasting of the interossei that occurs in the rheumatoid type of arthritis as seen in Figs. 13 and 14. There was limitation of movement in the elbows and the fingers, but the maximum deformity was in the hips. In these joints flexion was limited to 150°, abduction was 8 in. measured at the ankles, and rotation was absent. She walked with short rapid steps and a slight waddling gait. She had difficulty mounting stairs owing to the limitation of hip flexion.

There were no abnormalities in the cardiovascular, respiratory, nervous, gastro-intestinal, or genito-urinary systems.

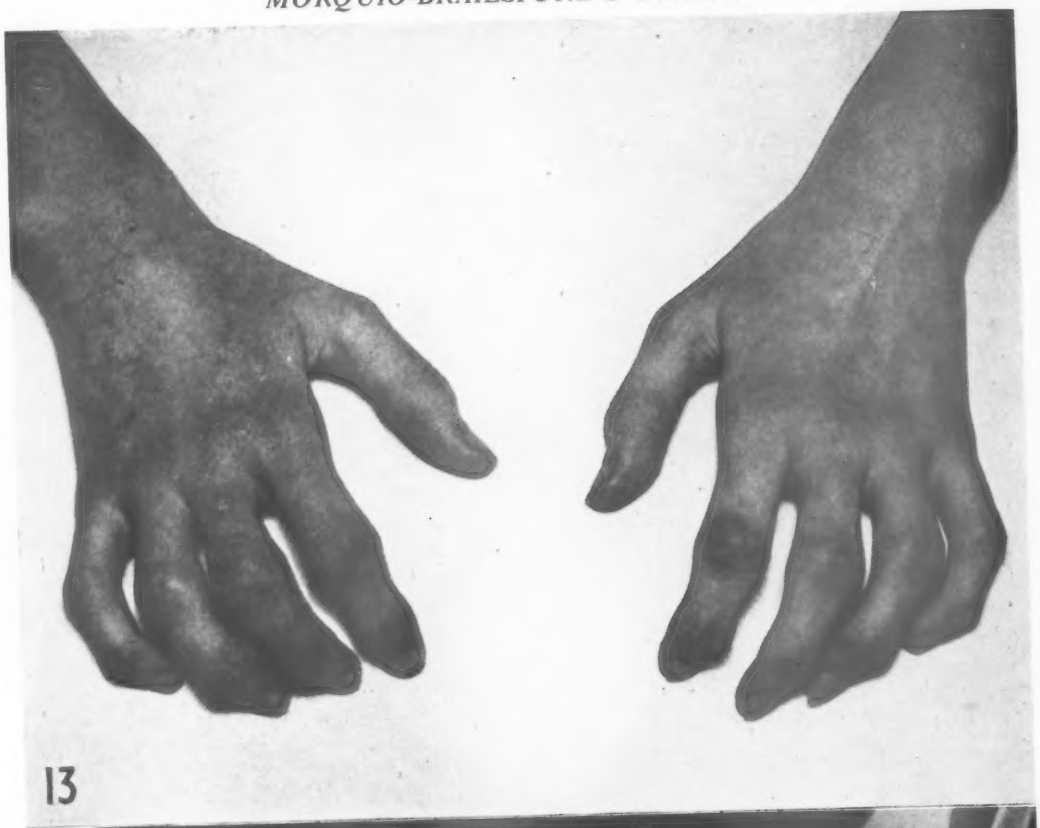
X-ray examinations of the whole skeleton (Dr. Grace Batten) revealed the following abnormalities :

Spine (Figs. 15, 16).—The vertical bodies are all characteristically flat and wide and most are irregularly ossified with typical anterior moth-eaten appearances and compressions.

Pelvis and Hips.—The pelvis is broad, oblique, and flattened, with incompletely developed epiphyses for the iliac crests. There is gross deformity of the femoral heads and acetabuli, and very short femoral necks (Fig. 17 : compare Fig. 10).

Hands and Feet (Figs. 14, 18).—The bones are short with irregular broad ends. The cortices are not thickened. The carpal and tarsal bones are rather large and show cortical density. The lower ends of the radii and ulnae are irregular. Radiographs of the hands show that the joint swellings are entirely articular, without any thickening of the periarticular tissues.

Elbows.—The ends of the bones are irregular, and all



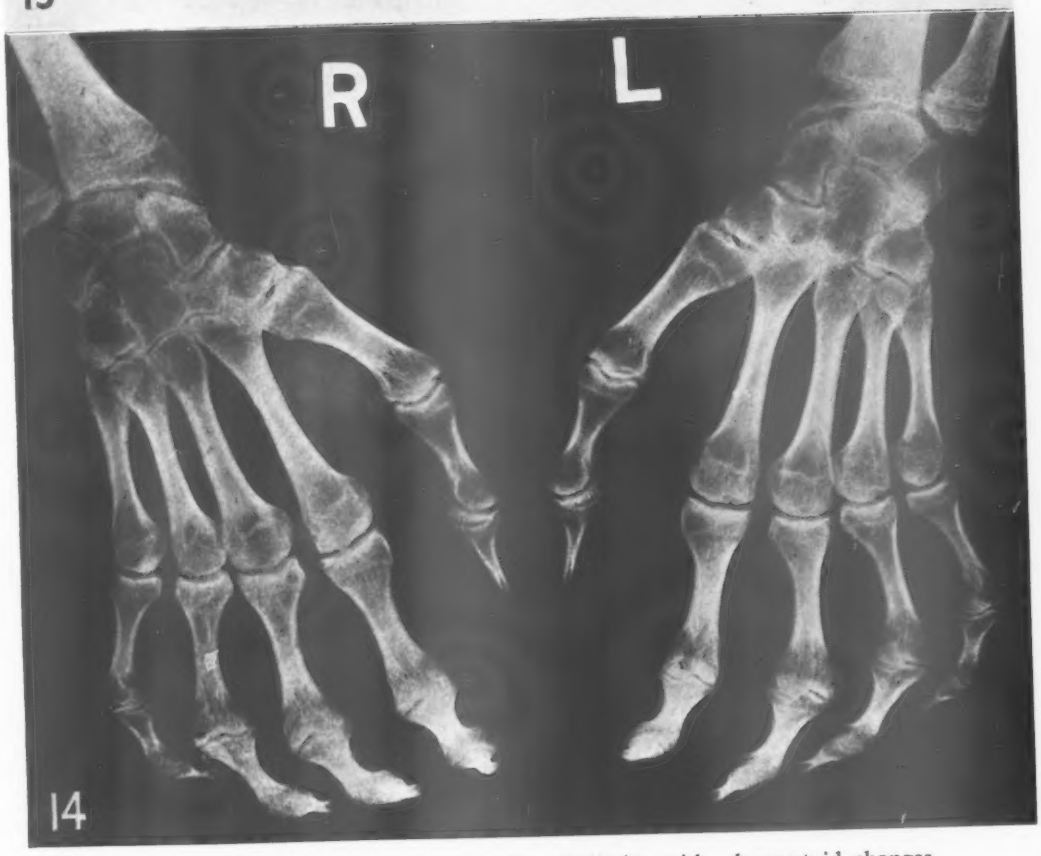
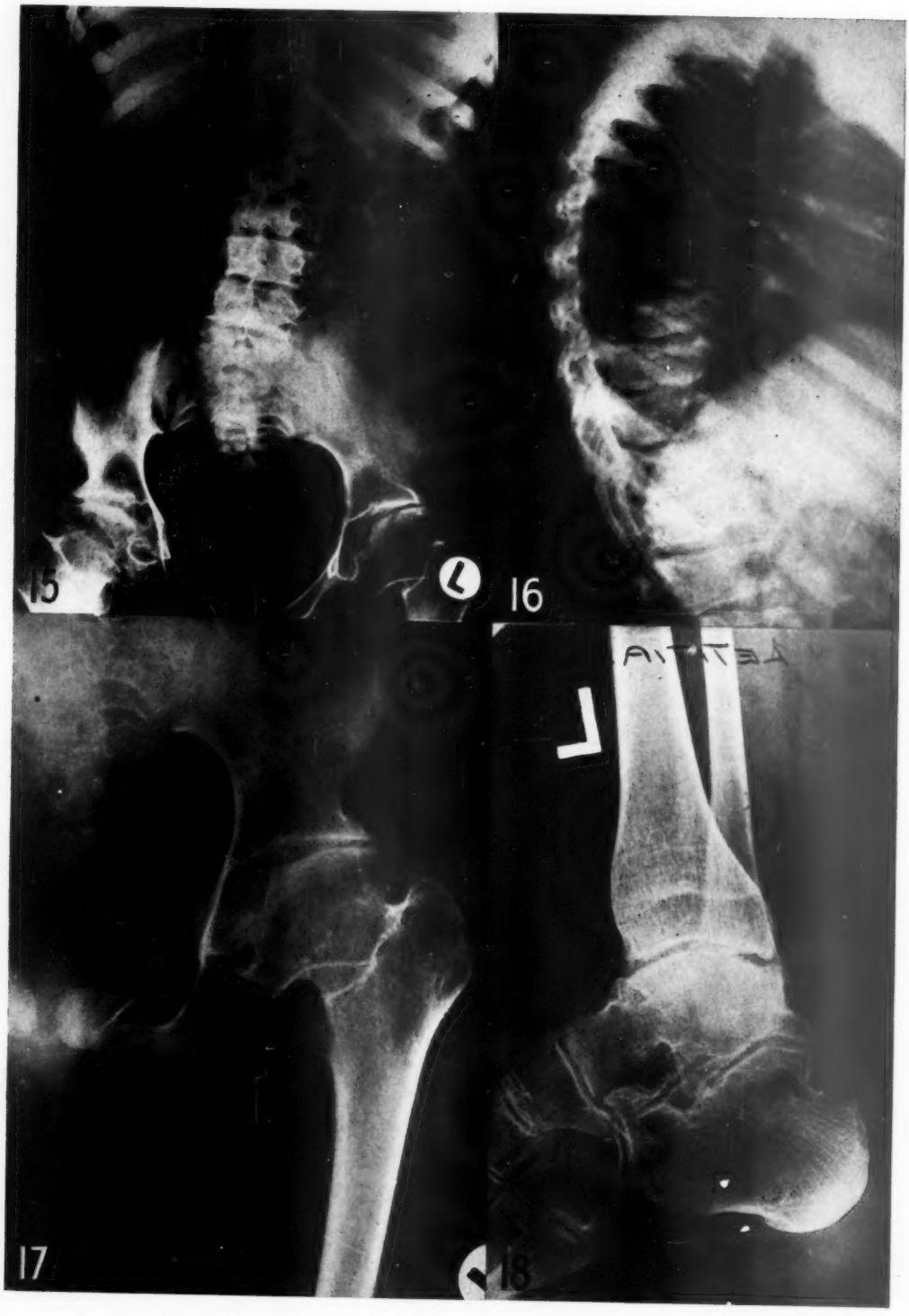


FIG. 13.—Hands of Case 2, showing similarity with rheumatoid changes.
FIG. 14.—Radiograph of hands, Case 2.



FIGS. 15, 16.—Radiographs of spine, Case 2. FIG. 17.—Radiograph of pelvis and hip, Case 2.
FIG. 18.—Radiograph of left ankle, Case 2.

the epiphyses (including the internal epicondylar) are united. The long bones are all splayed out at the ends and their extremities deformed and irregular.

Changes similar to these are seen in the knees and shoulders. There is generalized osteoporosis. The skull is normal.

The similarity of physical characteristics in these cases is striking. In both cases no disorder was noticed until the patients were about 5 years old, and then the main symptoms appeared as painless swellings of the joints and difficulty in walking which must have been due at first to the primary muscle weakness associated with this condition, rather than to the secondary degenerative joint changes which have appeared since.

Table 1 gives a comparison of certain physical measurements of each patient at the age of 16.

TABLE 1

PHYSICAL MEASUREMENTS OF CASES 1 AND 2 AT 16 YEARS

	Case 1	Case 2
Circumference of head ..	21·7 in.	22 in.
Standing height	52 in.	51 in.
Weight	75·5 lb.	78 lb.
Length of legs	29 in.	26 in.
Length of arms	19 in.	20 in.
Chest circumference ..	29 in.	30¼ in.
Chest expansion	1½ in.	1¼ in.

The faces of both these patients appear intelligent and seem to have developed normally and in advance of the remainder of their bodies.

Table 2 gives a summary of some of the laboratory investigations in both cases.

TABLE 2

LABORATORY INVESTIGATIONS, CASES 1 AND 2

	Case 1	Case 2
Red cells	4,980,000	3,600,000
Haemoglobin ..	93%	60%
White cells ..	16,200	6,250
	Normal differential count	Normal differential count
Sedimentation rate	8 mm. 1 hr. (Westergren)	7 mm. 1 hr. (Westergren)
Wassermann reaction ..	Negative	Negative
Serum calcium ..	11·1 mg.	7·88 and 8·32 mg.
„ phosphorus	2 mg.	3·44 and 3·74 mg.
„ alk. phosphatase	8·2 units	9·2 units
Plasma uric acid ..	2·6 mg.	2·4 mg.
„ urea ..	2·8 mg.	—

It is of interest that in the cases described by Morquio the serum calcium was low, but these figures were taken in younger patients, possibly while the disease was still active. There is no convincing reason to account for the differences in these cases.

The radiographic changes in both patients show marked similarity, as is to be seen in the reproductions ; the secondary degenerative changes in the hip joints are particularly noticeable.

The other factor which appears to be important aetiologically in this disorder is the consanguinity of the parents. In both these cases and in those described by Morquio the parents were first cousins.

Differential Diagnosis

These two cases undoubtedly correspond to the condition known as Morquio-Brailsford's disease or chondro-osseous dystrophy, and they seem to bear more similarity to Group B than to the other groups.

The condition may sometimes be confused with the rheumatoid type of arthritis, particularly when the hands are affected, as in these two cases. Fairbank, however, in a personal communication, informs me that in over sixty cases he has studied he has found that such a condition of the finger joints as exists in these two cases is exceptional ; he found it in only four cases. This does not of course mean that all the other cases had normal hands for, as he points out, thick metacarpals and rather stumpy fingers were not uncommon. One or two cases had some limitation of movement of the fingers, but did not present the striking picture seen in these two cases. Both the patients here described were thought to have rheumatoid arthritis until the generalized nature of the disease was discovered. The best means of differentiation from rheumatoid and degenerative joint disease is by *x*-ray examination, as the illustrations show. Clinically there is no pain in the development of these deformities, and there is no wasting of the interossei muscles. The swelling of the interphalangeal joints are articular rather than periarticular in origin, and involve the proximal and terminal joints. The disorder does not develop in the same manner as it does in rheumatoid or degenerative joint disease, and there is no real systemic upset. In their description, Meyer and Brenneman (1932) observed a case from the age of 10 months to 8½ years, and they stated that all the deformities which were apparent at the age of 8½ years were present when the child was first seen and had only become more obvious with the growth of the child. In Case 1 the deformities have been observed by the writer from 1933 to 1949 and there

is astonishingly little change, taking into account the time factor.

Other remote differential diagnoses, such as spinal caries, achondroplasia or endocrinal and metabolic causes of stunted development, are readily excluded by the appropriate investigations.

Comment

This disease is chiefly characterized by changes in the spine and hips, already outlined, and to a less extent by abnormality of epiphyseal development and abnormal and extra centres of ossification which unite prematurely. There must also be some abnormality of the epiphyseal plate to prevent its further growth and to cause the diaphysis to unite with the epiphysis. These abnormalities produce the apparent joint changes described above, and compare accurately with similar cases described. One of Morquio's cases, however, showed complete absence of the carpal bones, and thus an abnormal range of movement.

The hips, taking the main weight of the body, suffer the greatest deformities, as may be seen in the radiographs. The prognosis is not improved by the possibility that secondary degenerative joint disease may be superimposed on the original damage to the epiphyses. The hips, which are the most damaged joints, suffer most. The possibility of a vitallium cup arthroplasty operation to relieve the hip-joint condition might be considered.

It is possible that, had the second case been kept in bed with both legs extended, the joint abnormalities might have been diminished before the epiphyses united, but such treatment would in all probability have had to be continued for years.

Summary

Two cases are reported of chondro-osseous dystrophy showing the typical limitation of stature, the short trunk with disproportionately long limbs, and joint abnormalities arising in the epiphyses.

There was consanguinity of the parents in both cases. This fact appears to be the most constant finding in all similar cases reported.

A possible confusion with rheumatoid disease, especially where the hands are involved, is particularly noted.

I should like to express my indebtedness to my former house physician, Dr. L. S. Sacher, for much help in collecting the material necessary for the preparation of this paper and particularly in connexion with Case 2. I am also indebted to Dr. William Mackenzie of Newcastle and to Sir Thomas Fairbank for referring Case 2 to me, and to Dr. Grace Batten for her help with the radiographs.

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Maladie de Morquio-Brailsford Simulant les Manifestations Arthritiques de la Maladie Rhumatismale

Résumé

On relate deux cas de dystrophie chondro-osseuse présentant la limitation typique de la taille—le tronc court et les membres incommensurablement longs—ainsi que des anomalies articulaires d'origine épiphysaire. Dans les deux cas il y avait la consanguinité des parents. Il semble que ce fait est le plus constamment trouvé dans tous les cas similaires relatés. On note particulièrement la possibilité de confusion avec la maladie rhumatismale, surtout là où les mains se trouvent atteintes.

EFFECT OF BLOOD TRANSFUSION ON RHEUMATOID ARTHRITIS

BY

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Introduction

Blood transfusion as a method of treatment of rheumatoid arthritis has been employed by Copeman (1931a, b), Holbrook and Hill (1936), Hench (1938), Hartung (1943), Appelqvist and Holsti (1947), and others. The aim of this investigation was to find the effect of transfusions of whole blood, concentrated red cells, and plasma on the blood and general condition of patients suffering from the rheumatoid type of polyarthritis.

The patients were those normally admitted to the Royal National Hospital for Rheumatic Diseases, Bath, during 1948. No special selection was made, but most had moderately or very severe illness.

Serial plasma protein estimations, sedimentation rates, crude and corrected suspension stability (C.S.S.) readings, haematocrit readings, and haemoglobin estimations were made in all cases, and red cell counts were done when it was thought they might be useful. The tests were done in the first place before transfusion, and thereafter at weekly intervals. As far as possible experimental errors were eliminated ; for instance, one person was responsible for each estimation during the whole period and the technique was standardized. The biuret method was used for the estimation of the plasma proteins, and the suspension stability was estimated by the Spa method of Collins and others (1939).

The Bristol depot of the National Blood Transfusion Service supplied the whole blood, packed cells, and plasma used in these investigations, and accurate assessment of group Rh and other factors were made in every case. No severe transfusion reaction was ever noted, but a mild rigor occurred in four cases. Usually each transfusion consisted of 2 pints of packed red cells or whole blood. The majority of patients had only one transfusion, but this was repeated in some cases where it was considered necessary, and a few patients had three separate transfusions.

Controls on 25 normal people gave the following results :

Plasma Proteins :
Total Protein 5·8-8·6 g. %.
Fibrinogen 0·1-0·4 g. %.
Albumin 3·0-6·5 g. %.
Globulin 0·9-2·5 g. %.
$\frac{A}{G}$ ratio 4 : 1-1·2 : 1.
Haemoglobin 100%-14 g. standard.
Haematocrit 42-45%.
Sedimentation Rate (Wintrobe, crude)—
0-15 female, 0-10 male.
C.S.S. 85-95%.

Initial Plasma Proteins in Sixty Patients

Complete plasma protein estimations were carried out on sixty patients with rheumatoid arthritis. The fibrinogen values were high in thirty-eight, high normal in sixteen (0·4 per cent.), and well within normal limits in six cases only. The globulin content was raised above 2·5 g. in twenty-one cases, ten also having a lowered albumin value, while in thirty-nine normal values were obtained. The patients with raised globulin and lowered albumin figures had a severe form of the disease as measured by extent of involvement, pain, loss of weight, anaemia, and C.S.S., but some patients whose plasma proteins were within normal limits were also as severely affected. All patients showed secondary microcytic anaemia of varying severity, and abnormal crude and corrected erythrocyte sedimentation rate (E.S.R.).

Effect of Transfusion on Fifty Cases

Fifty cases have so far been treated by transfusion and adequately followed up biochemically and clinically. Forty were given transfusions of packed cells or whole blood, and ten have been given plasma transfusions, three of these subsequently having a

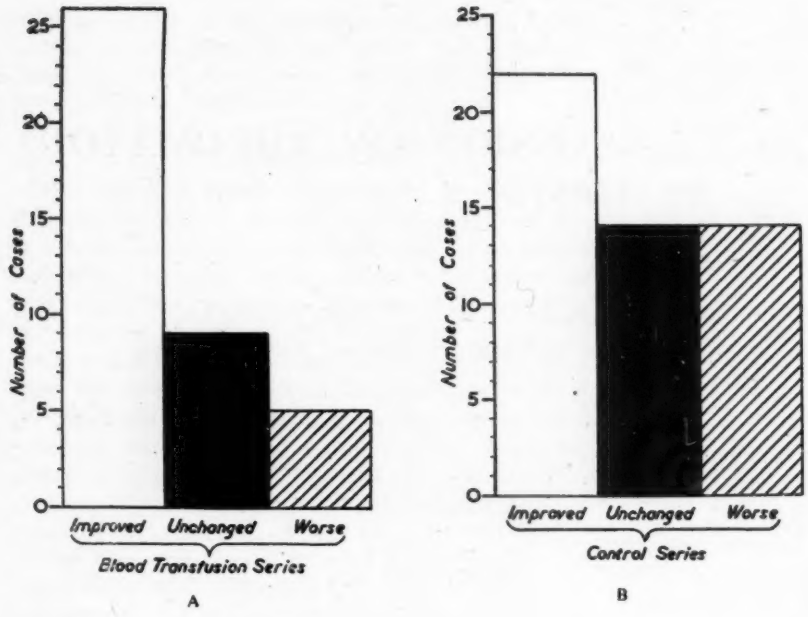

FIG. 1.—Crude sedimentation rate. Blood transfusion series forty cases; controls fifty cases. All were followed up for six months.

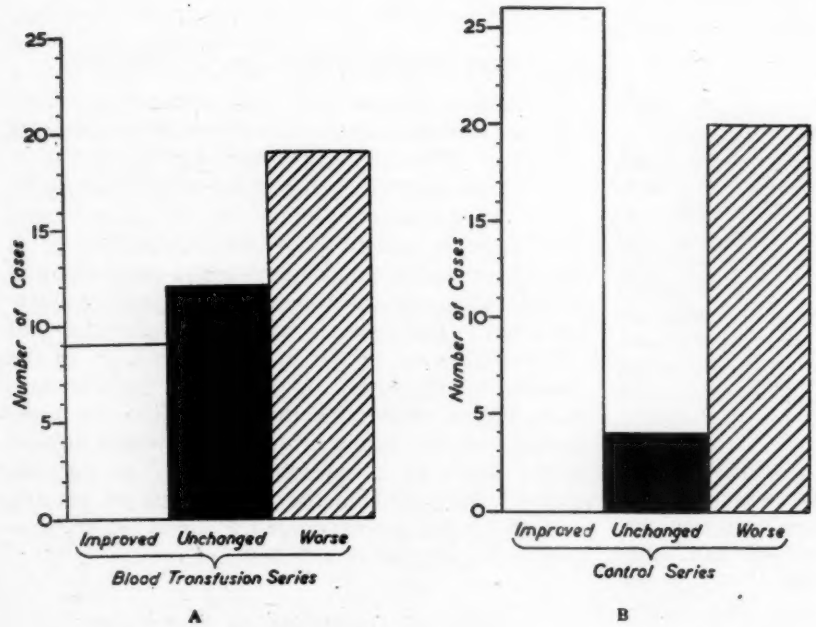

FIG. 2.—Corrected suspension stability in the two series.

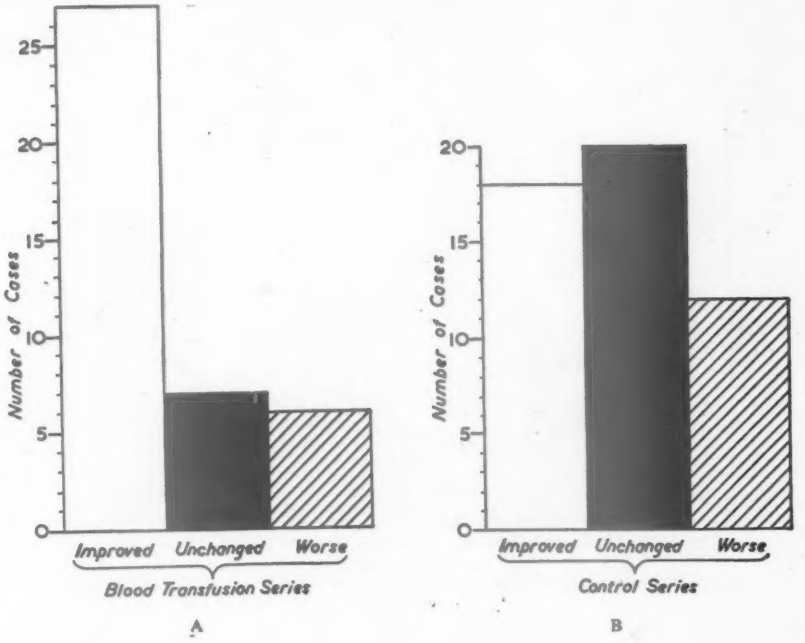

FIG. 3.—Haematocrit in the two series.

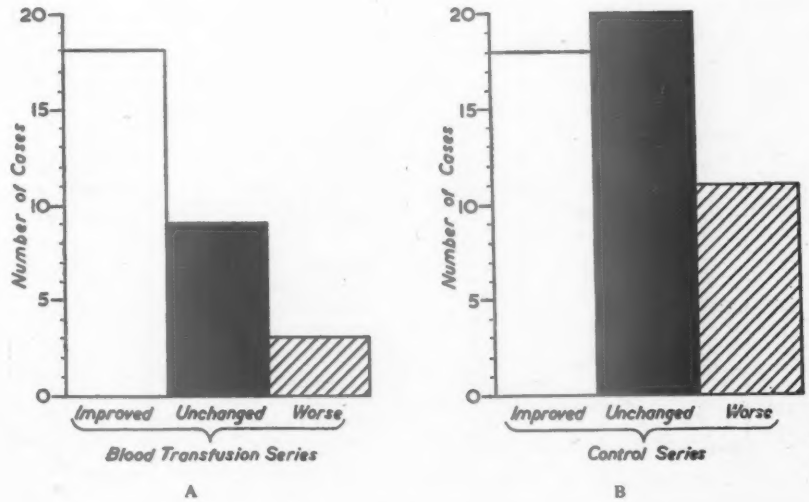

FIG. 4.—Weight in the two series (ten cases were not recorded in the blood transfusion series, and one case was omitted from the controls).

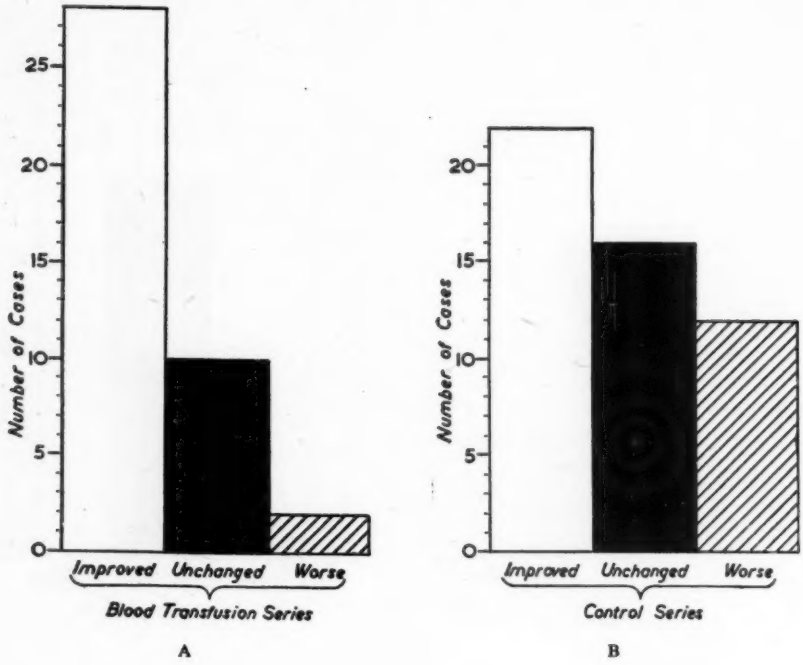

FIG. 5.—Clinical assessment in the two series.

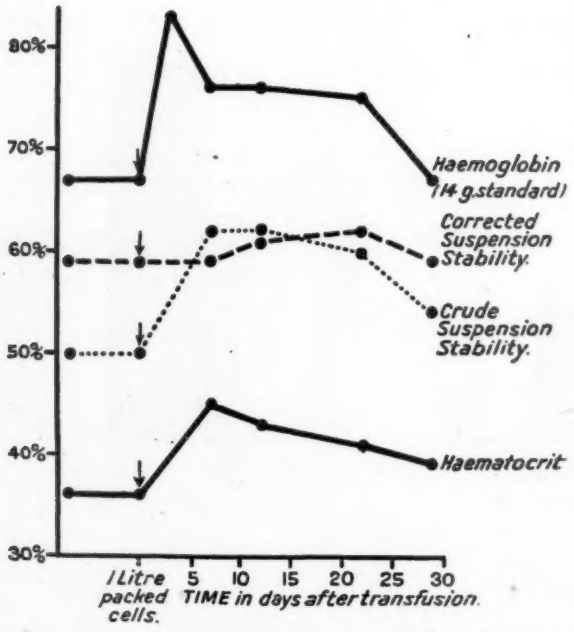

FIG. 6.—Cases with normal plasma protein values before and after transfusion with one litre of packed red cells (twenty-six cases).

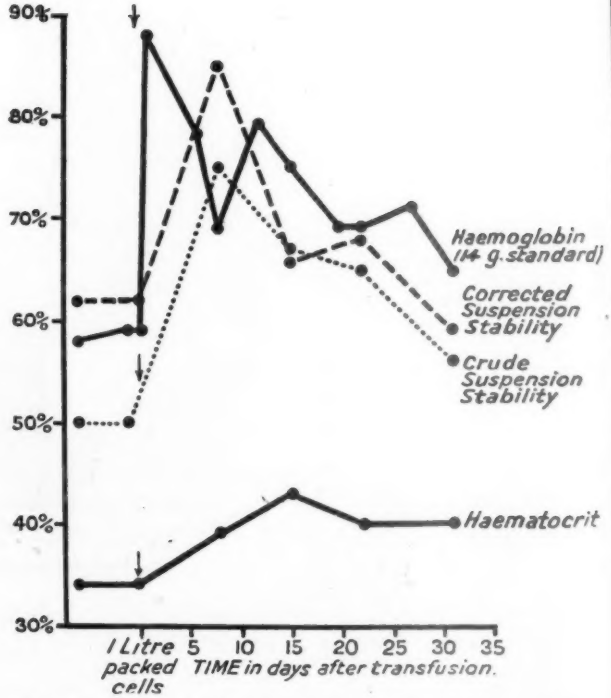

FIG. 7.—Cases with abnormal plasma protein values becoming normal after transfusion with one litre of packed red cells (eleven cases).

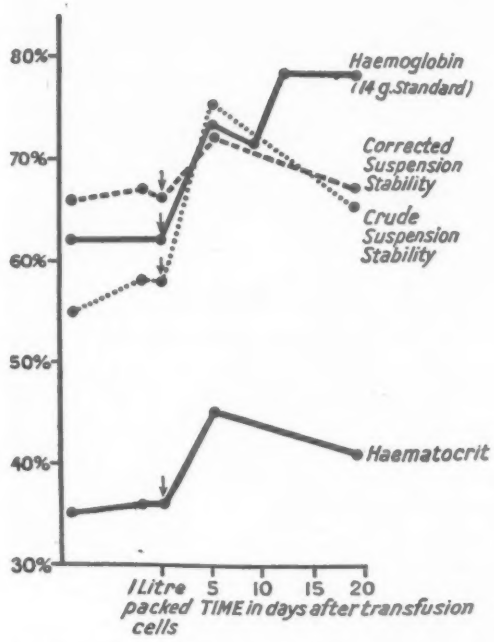

FIG. 8.—Cases with normal plasma protein values becoming abnormal later (nine cases).

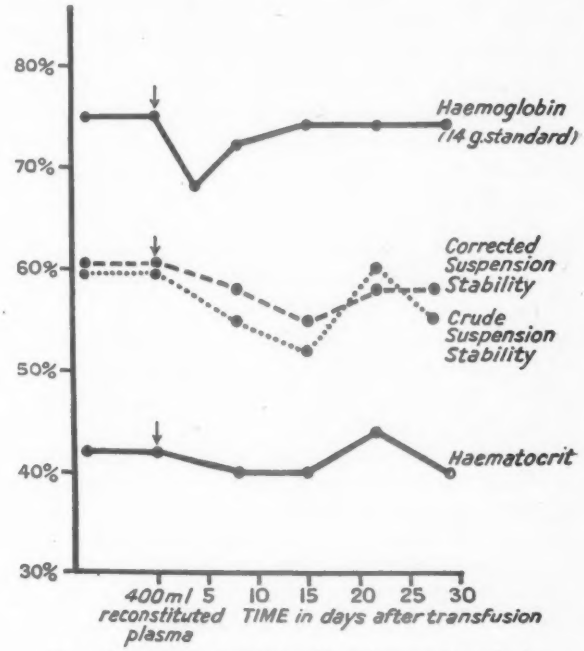

FIG. 9.—Cases treated with plasma transfusion (ten cases).

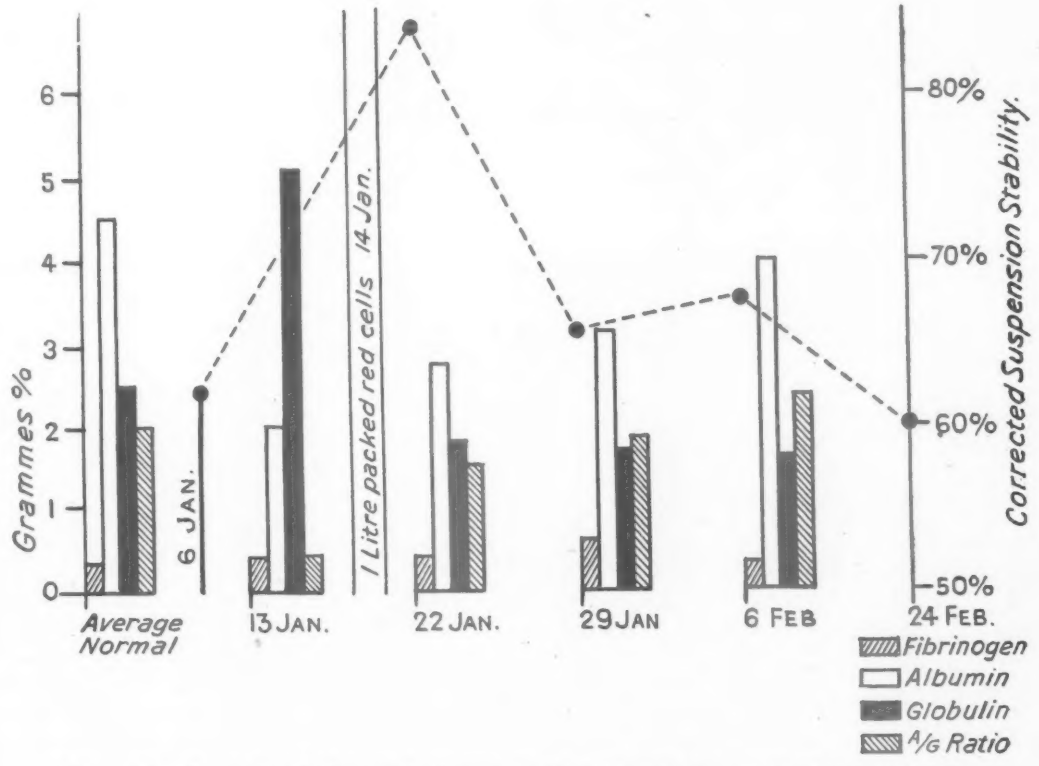

FIG. 10.—Example of abnormal plasma proteins becoming normal after transfusion.

transfusion of packed cells. All patients who were transfused with blood showed an improvement in the levels of haemoglobin, E.S.R., C.S.S., and haematocrit. This occurred within forty-eight hours after transfusion and had returned to, or nearly to, the previous abnormal value twenty-eight days later. The patients who were transfused with plasma alone showed no improvement in these levels.

Before transfusion, sixteen patients had abnormal plasma proteins with a high globulin, and nine had also a low albumin. Fourteen of these had transfusions of packed cells or whole blood, and two had transfusions of plasma only. Of the fourteen, eleven showed a return to normal protein values during the week after transfusion. At the same time the C.S.S. showed an improvement in all except the three patients in whom the plasma proteins remained abnormal after transfusion. In the two patients with abnormal proteins who were given plasma only, the plasma proteins remained abnormal after transfusion and no improvement in any blood tests was noted. In thirty-four patients where the plasma proteins were at first normal, twenty-six were given transfusions of packed cells or whole blood, and eight were given transfusions of plasma. In only five cases was there any improvement in the C.S.S., and even then this was not so marked as in those eleven cases where a reversal of the abnormal plasma proteins ratio occurred after transfusion.

Where the C.S.S. showed improvement, this was maximal seven to ten days after transfusion and appeared to drop back towards the previous abnormal figure fourteen to twenty-one days afterwards. In nine cases where the plasma proteins were normal before transfusion, abnormal figures occurred afterwards but never within fourteen days of transfusion. The three patients who were given plasma originally and showed no improvement, when subsequently given blood transfusions showed the usual improvement in the blood tests.

In thirty-two cases serum and plasma gel tests were carried out. There seemed to be no correlation between the quantity of the plasma proteins and the reaction to these tests, which appear to be related more to an abnormal state of the plasma colloids than to a quantitative increase of any one protein.

All patients who were given blood transfusions showed clinical improvement, the patients stating that they felt stronger, suffered less pain, and were more fit to undergo the other treatments prescribed. Smooth atrophic skin, cyanosis, coldness, and excessive sweating of the extremities were not infrequently improved after transfusion. No immediate change in the appearance of the arthritis, either clinically or radiologically, was apparent.

Six Months' Follow Up

So far it has been possible to review fifty patients who have been readmitted to hospital. Forty of these had had blood transfusion, seven plasma, and three plasma and blood. The results shown in Tables 1 to 3 have been obtained, an allowance of

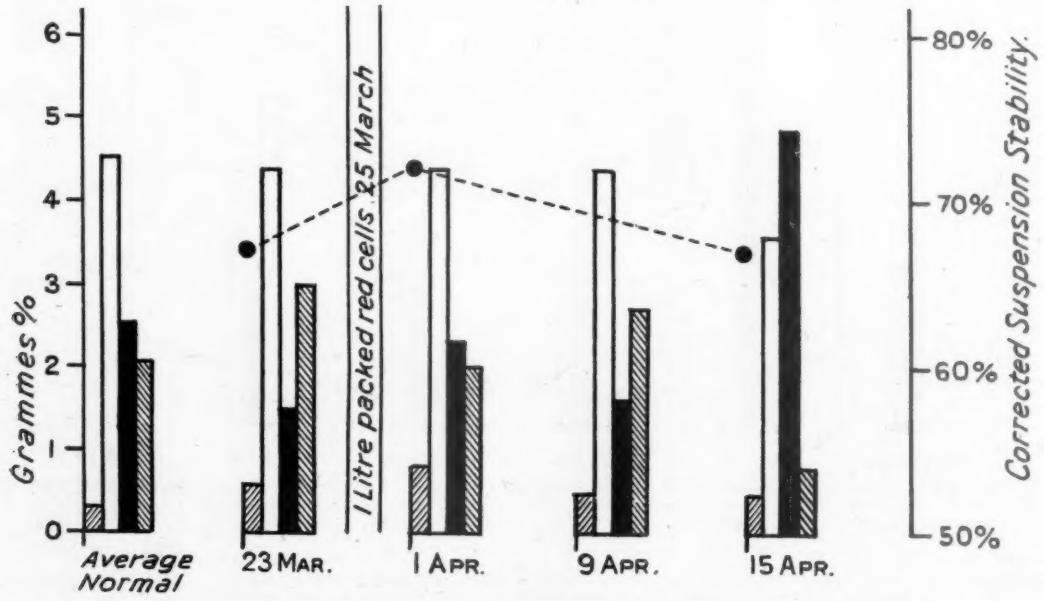

Fig. 11.—Example of normal plasma proteins becoming abnormal after transfusion.

±2 having been made throughout as the likely margin of error (± 4 lb. in the case of weight).

Twenty-seven cases who were transfused with blood have not returned to hospital, and these have been circulated with a questionnaire : twenty-two report an improvement in their state, three report no change, and two were worse since their last admission with transfusion.

TABLE 1

RESULTS IN FORTY CASES TRANSFUSED WITH PACKED CELLS OR WHOLE BLOOD

	Crude E.S.R.	C.S.S.	Hb	Haemato-crit	Weight*	Clinical assess-ment
Improved ..	26	9	31	27	18	28
Unchanged	9	12	4	7	9	10
Deteriorated	5	19	5	6	3	2

* In ten cases the result was not recorded.

Control Series

This series was compared with fifty patients with a similar type of rheumatoid arthritis who were treated at the Royal National Hospital for Rheumatic Diseases, Bath, during 1948, in exactly similar ways, but who did not have blood or plasma transfusions. The results in the control series are shown in Table 4.

Conclusions

From the follow-up, the following facts emerge. The crude sedimentation rate appears to be better in the series given blood transfusion than in the control series, and there appears to be no significant difference in the values of the corrected sedimentation rate or weight between those who had been given blood transfusions and those who had not.

The haematocrit levels were better in those who had been given a transfusion, and the clinical assessment was better in those who had been given

TABLE 2

RESULTS IN SEVEN CASES TRANSFUSED WITH PLASMA

	Crude E.S.R.	C.S.S.	Hb	Haemato-crit	Weight*	Clinical assess-ment
Improved ..	2	2	1	4	2	3
Unchanged	2	—	4	1	4	4
Deteriorated	3	5	2	2	—	—

* One case was not recorded.

a transfusion. This is in agreement with our general impressions during the past year.

The results of the plasma protein estimations are difficult to assess, and a larger number will have to be done before any definite conclusions can be

TABLE 3

RESULTS IN THREE CASES TRANS USED WITH PLASMA AND BLOOD

	Crude E.S.R.	C.S.S.	Hb	Haemato-crit	Weight*	Clinical assess-ment
Improved ..	2	1	3	1	—	1
Unchanged	1	1	—	2	2	1
Deteriorated	—	1	—	—	—	1

* One case was not recorded.

reached. We have confirmed that in a certain number of cases the plasma proteins are disturbed, and in certain of these cases blood transfusion appears to return these values to normal.

Plasma transfusions in the cases we have treated appear to have no effect either on the blood chemistry or on the disease process.

The arthritic condition appears to be little affected by blood transfusion, and it is on the general state of health that the greatest effect is noticed. We therefore believe that this form of therapy is not specific, but is a useful supporting measure and merits much greater use.

Our indications for transfusion are as follows : (1) a haematocrit below 35 per cent., or alternatively a haemoglobin reading below 60 per cent. ; (2) an active condition which does not react to other forms of treatment ; (3) where it is considered that a patient is not fit, on account of his general condition,

TABLE 4

RESULTS IN THE CONTROL SERIES

	Crude E.S.R.	C.S.S.	Hb	Haemato-crit	Weight*	Clinical assess-ment
Improved ..	22	26	3	18	18	22
Unchanged	14	4	1	20	20	16
Deteriorated	14	20	5	12	11	12

* In one case the result was not recorded.

for other treatments considered necessary, such as aurotherapy, balneotherapy, manipulation under general anaesthesia, or other operative interference.

Summary

The effect of transfusions of blood and plasma on patients suffering from rheumatoid arthritis is described.

The haematological tests done in each case are enumerated, together with results in twenty-five normal controls.

In sixty cases in which the plasma proteins were estimated initially, fibrinogen values were high in thirty-eight, high normal in sixteen, and within normal limits in only six cases ; globulin values

were high in twenty-one cases, ten of these showing a concomitant low albumin figure.

All patients showed secondary microcytic anaemia of varying severity, and abnormal crude and corrected erythrocyte sedimentation rates.

Fifty patients have been treated by transfusion and adequately followed up. Forty have been given blood transfusions, and ten plasma, three of the latter later having blood in addition.

All patients given blood showed an immediate improvement in levels of haemoglobin, haematocrit, and erythrocyte sedimentation rate. This occurred within forty-eight hours of transfusion, and had returned to, or nearly to, the previous abnormal value twenty-eight days later. Cases given plasma alone showed no improvement in these estimations.

Of fourteen patients with abnormal albumin and globulin figures initially who were given blood, eleven showed normal values during the week after transfusion. In two similar patients given plasma only, no such change was observed.

Serum and plasma gel tests showed no correlation between protein abnormalities and test reactions.

Fifty patients have been reviewed six months later on readmission to hospital and compared with fifty similar patients who had been treated in exactly similar fashion with the exception of blood transfusion. There was no significant difference in the values of corrected suspension stability or weight in the two series, although the crude erythrocyte sedimentation rate was better for the blood transfusion series. The haematocrit levels and clinical assessment showed a much better figure for those given blood transfusions.

The indications for blood transfusion in rheumatoid arthritis are described. It is considered that it is on the general condition of the patient that the greatest effect is noticed, and the arthritis is not much affected by transfusion. It is suggested that it is a useful supporting measure and merits greater use in this disease.

We should like to thank Dr. H. J. Gibson for his help in this investigation, Mr. E. W. Richardson, and Mr. D. S. Bidmead for assisting in the pathological investigations. We are also grateful to the Editor of the Proceedings of the Royal Society of Medicine for permission to publish figures.

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Effet de la Transfusion du Sang sur l'Arthrite Rhumatismale

Résumé

On décrit l'effet de la transfusion du sang et du plasma sur des malades atteints d'arthrite rhumatismale. On énumère les épreuves hématologiques dans tous les cas, ainsi que les résultats chez 25 témoins normaux.

Sur 60 malades chez qui les protéïnes du plasma furent préalablement déterminées, les chiffres du fibrinogène étaient élevés chez 38, près de la limite supérieure normale chez 16 et endéans les limites normales chez 6 seulement ; les chiffres de la globuline étaient élevés chez 21, dont 10 présentaient une diminution concomitante de l'albumine.

Tous les malades présentaient une anémie microcytique secondaire de sévérité variable et leur sédimentation globulaire, brute et corrigée, était anormale.

Cinquante malades furent traités par la transfusion du sang et étudiés d'une façon appropriée. Quarante d'eux reçurent du sang total et dix du plasma ; trois de ces derniers reçurent plus tard du sang en plus.

Chez tous les malades transfusés il y eut une amélioration immédiate portant sur le niveau de l'hémoglobine, le volume corpusculaire et sur la sédimentation globulaire. Ceci eut lieu quarante huit heures après la transfusion ; vingt huit jours plus tard on constata un retour aux chiffres antérieurs, ou à peu près. Chez ceux qui reçurent rien que du plasma on ne vit aucune amélioration de la formule sanguine.

Chez onze malades sur quatorze, chez qui les chiffres d'albumine et de globuline avaient été anormaux, ces chiffres devinrent normaux au cours de la semaine qui suivit la transfusion. On n'observa aucune modification chez deux malades similaires qui reçurent du plasma seulement.

On ne trouva aucun rapport entre les anomalies de la formule sanguine et les résultats des épreuves colloidales pour le sérum et le plasma.

Cinquante malades furent re-examinés 6 mois plus tard lors de leur retour à l'hôpital et ils furent comparés aux cinquante malades similaires traités d'une façon exactement similaire, à l'exception de la transfusion sanguine. On ne trouva aucune différence significative entre ces deux groupes en ce qui concerne les chiffres corrigés de la stabilité de la suspension ou le poids ; toutefois la sédimentation globulaire brute fut meilleure chez les transfusés. De même, la détermination du volume corpusculaire et l'examen clinique donnèrent un résultat meilleur chez les transfusés.

On décrit les indications de la transfusion du sang dans l'arthrite rhumatismale. On considère que le meilleur effet est produit sur l'état général du malade et que l'arthrite est à peine influencée par la transfusion. On suggère que c'est une mesure adjuvante utile et qu'elle mérite une application plus fréquente dans cette maladie.

STIMULATION OF THE SUPRARENAL GLANDS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

PRELIMINARY REPORT

BY

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Since the publication of the report of the Mayo Clinic workers (Hench and others, 1949) on the spectacular improvement of rheumatoid arthritis under the influence of cortisone (17-hydroxy-11-dehydro-corticosterone) or of adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland, attention has been concentrated on the problem of the production of these hormones. The present output of cortisone and ACTH by the manufacturers is very limited, and the cost of the treatment by these compounds prohibits the possibility of prolonged medication, especially as this treatment may be used in the future much oftener than, for example, insulin in the treatment of diabetes mellitus, rheumatoid affections being much commoner.

The physiopathology of the adrenal glands fascinated physiologists and clinicians in the past as much as it now intrigues general physicians. Cannon and others (1924) first proved in experiments on dogs that adrenaline is abundantly dissipated from the adrenals as a result of hypoglycaemic action of insulin, which they described as an emergency measure for an emergency state. Since this publication many papers on this subject have appeared confirming Cannon and his co-workers' findings in a great variety of experiments. It has been found that repeated insulin injections causing hypoglycaemia are able to precipitate hypertrophy and hyperfunction of the adrenal cortex in rabbits (Langecker, 1928 ; Radall, 1940 ; Godlowski, 1947 ; and many others), in mice (Goormaghtigh, 1931; and many others), and in pigeons (Miller and Riddle, 1941). In rabbits (Godlowski, 1947) the adrenal cortex responded to repeated insulin hypoglycaemias with hypertrophy more or less to the same degree as the medulla. It was also shown that this hypertrophy of the whole gland ran parallel to the hyperfunction of the medulla, which was characterized by increased content of the adrenaline in the whole suprarenal gland. This functional hypertrophy of the total gland persisted throughout the whole observation period, that is, for thirty days after the last hypoglycaemia (Figs. 1, 2, 3, 4, pp. 290-1).

Apart from these experimental observations it was also found (Godlowski, 1946 ; 1948a) that intravenous adrenaline infusion or insulin hypoglycaemia in normal individuals or in allergic patients caused a substantial drop in the absolute amount of eosinophilic cells in the peripheral blood. Similar changes were noticed when ACTH or cortisone was applied (Thorn and others, 1948). In 1944 Vogt found that " intravenous infusion of adrenaline causes a strong, immediate and long lasting stimulation of suprarenal activity in the eviscerated dog and cat. The effect was obtained with doses of adrenaline which occur in the body under physiological conditions. The increased yield was of the order of several times the basal output. This action is independent of blood pressure or blood flow, and is not mediated by a hormone from pituitary ".

These somewhat scattered observations can be closely correlated in the following way : adrenaline intravenously infused into human patients (Godlowski, 1948a) acts similarly to the adrenaline used by Vogt (1944) in the perfusion experiments causing increased output of cortical hormone which in turn causes eosinopenia (Thorn and others, 1948). On the other hand large doses of insulin administered to allergic patients (Godlowski, 1946; 1948a) precipitates the regulating mechanism of adrenaline liberation, which again in turn stimulates the output of cortical hormones ; in other words, by using intravenous adrenaline infusion or insulin hypoglycaemia one can directly or indirectly stimulate adrenocortical function applying a transitory, mild emergency state, which one can call a sub-physiological stimulation to the adrenal cortex in contrast to the physiological one caused by ACTH.

The Present Experiments

With these experimental observations in mind, one case of rheumatoid arthritis has been treated with intravenous adrenaline infusions and with insulin hypoglycaemia according to the technique described elsewhere (Godlowski, 1947; 1948a), and finally by subcutaneous injections of adrenaline suspended in oil. One case of acute muscular rheumatism and one case of acute fibrositis treated with adrenaline in oil suspension is also presented.

Case 1.—A man aged 41, a Regular Army N.C.O., married, had his first attack of rheumatoid arthritis in 1941; the left knee and right wrist joints were affected. During the past eight years he had several recurrences of rheumatoid episodes in various joints. He was treated with sodium salicylate, aspirin, penicillin, T.A.B. vaccine, milk injections, and physiotherapy in various forms and on many occasions, with variable results; but pain and stiffness in joints and muscles were permanently present. In September 1948, he was admitted to Ballochmyle Hospital with gross deformity of both wrists, of the metacarpo-phalangeal joints of both hands, and in the right elbow and both knee joints. The muscles of hands, forearms, and calves were grossly wasted, and there was moderately severe periarticular oedema around the affected joints. Passive and active movements in the affected joints caused excruciating pain. The muscular power of the affected limbs was very poor. The patient had no temperature and a poor appetite. The blood sedimentation rate was: first hour 59mm., second 85 mm. White blood cells numbered 7,600 per c.cm. of blood, and red cells 4,000,000. Hb was 14 g. There was no gross abnormality in the differential cell count, nor in the urine. Radiographs of the affected joints were typical of rheumatoid arthritis. A total dose of 1 g. of myochrysine was given. Physiotherapy in the form of heat and light massage resulted in some improvement. In May 1949, while the patient was in hospital, he suffered a severe exacerbation in the left knee joint with effusion, pain, and stiffness in the other affected joints. There was no fever. The blood sedimentation rate was 37, 65. The leucocyte and differential counts were within normal limits, red cell count and Hb remaining as before. The gold therapy had to be discontinued on account of toxic dermatitis, which was alleviated by BAL injections.

On July 21, 1949, treatment with adrenaline infusions and insulin hypoglycaemia was begun.

Intravenous Adrenaline Drip.—Adrenaline, 10 mg. in 600 ml. of normal saline, was infused at the rate of from 12 to 5 drops per minute for nine hours. The blood pressure, at first 120/80 mm. Hg, rose in thirty minutes to 180/100, and when the rate of infusion was slowed down it returned in twenty minutes to its previous level. Light palpitation and tremor accompanied the rise in blood pressure. In the next adrenaline infusions only 5 mg. was used, and this caused no subjective or objective disturbances of any significance. The slight tachycardia observed in the first infusion did not occur on other occasions. Owing to phlebitis of the infused veins adrenaline infusions had to be discontinued.

Insulin Hypoglycaemia was produced by subcutaneous injections of soluble insulin, starting with 25 units and gradually increasing to 80. A mistake was made in the last four treatments, and the patient received only 50 units of insulin, which did not produce any hypoglycaemic symptoms. On Aug. 7 the blood sedimentation rate was 19, 40, the oedema had practically disappeared, there was no pain, and passive and active movements were restricted only by the osseous deformities, which remained unchanged (Figs. 5, 6, p. 292). The red cell count was 5,000,000 per c.mm. of blood, and Hb was 15 g. The adrenaline drip having been discontinued and a mistake having been made with the insulin dosage, the patient remained for six days practically without treatment. On the seventh day of this therapeutic gap the sedimentation rate rose to 28, 54, but pain and oedema did not reappear.

The patient's weight before treatment was 10 st. 4 lb.; after fourteen days of treatment it was 10 st. 12 lb.

On Aug. 15, 0·1 per cent. adrenaline solution, 1 ml. five times daily, was injected subcutaneously. After seven days of this treatment the sedimentation rate rose to 36, 80, and pain and stiffness in joints and muscles reappeared. Palpitation, tachycardia, and light precordial pain began to trouble the patient. From Aug. 23 for seven days the patient received subcutaneous injections three times daily of 0·5 ml. adrenaline suspended in oil (Parke, Davis and Co.; 1 ml. contains 2 mg. of adrenaline). After this the sedimentation rate dropped to 17, 35, and pain and stiffness of muscles and joints once more disappeared. The patient remained in this condition for four weeks, that is, up to the time of the preparation of this paper.

Case 2.—A man aged 42, an electrician, for two years complained of recurrent attacks of muscular rheumatism and was treated with salicylates, gold injections, penicillin, and various types of physiotherapy. When the patient was seen he had had five days of pain and stiffness in the left lumbar region and thigh, which had immobilized him completely. The temperature was 100° F., and the pulse rate 110 per minute. He sweated profusely. Analgesics brought only temporary relief. Examination discovered severe pain and stiffness in the affected regions with grossly restricted passive and active movements. The sedimentation rate was 19, 49. Leucocytes numbered 10,000 per c.mm. of blood, and the differential count was within normal limits. At the end of seven days' treatment with adrenaline in oil suspension, 0·5 ml. injected subcutaneously three times a day, pain and stiffness disappeared completely, the sedimentation rate dropped to 9, 16, and the leucocyte count to 6,700 per c.mm. of blood. Insomnia occurring during treatment was relieved by light hypnotics.

Case 3.—A charwoman, aged 41, had complained for six years of recurrent attacks of acute fibrositis with pain and stiffness of the affected groups of muscles. When examined she had had for ten days an attack of severe pain in both shoulders and arms. There was pain on

pressure of the affected muscles and on movement of shoulder and elbow joints. The temperature, sedimentation rate, leucocyte, and differential counts were normal. A seven-day course of adrenaline in oil suspension, 0·5 m. injected subcutaneously three times a day, completely removed the pain and stiffness.

Discussion

The cases of rheumatoid arthritis and acute muscular rheumatism above described, which were treated with adrenaline infusions and insulin hypoglycaemias, and in the later stages with subcutaneously injected adrenaline suspended in oil, did not show the dramatic improvement in the course of the disease that American authors have described as taking place on treatment with cortisone and ACTH. It seems obvious that the application of the active hormone itself, or the use of physiological stimuli for the natural production of cortical hormone, should, on theoretical grounds, be more effective than the subphysiological stimulation described above. However, the obvious improvement in subjective and objective findings resulting from twenty-eight days' treatment of a case of advanced rheumatoid arthritis of a few years' duration, and from a short course of treatment in two cases of acute muscular rheumatism, justifies the hope that it may serve as a temporary therapeutic measure until the active hormone itself can be available for general use. The relief in pain, the increased passive and active movements in the affected joints and muscles, the striking improvement in muscular tonus and strength, the improvement in appetite and increase in body weight, the significant decrease in periarticular oedema, and the parallel improvement in laboratory findings, such as significant diminution of the sedimentation rate and the return to normal in red cell counts and Hb values, justify a further and more extensive trial, which should be undertaken before any conclusive assessment of this method can be passed.

The treatment with intravenous adrenaline infusions and insulin hypoglycaemias has, however, certain drawbacks. Both must be carried out in medical units where nurses have been adequately trained in handling hypoglycaemic patients. The hypoglycaemia need not be carried to the level of complete unconsciousness, as is done in the treatment in psychiatric cases. A level at which there is evident clinical hypoglycaemia in the form of profuse sweating, tremor, palpitation, general profound weakness and drowsiness, with voluntary muscular movements, superficial and deep reflexes, and contact with surroundings maintained, is sufficient for the production of the mild emergency state necessary for the development of countermeasures in the form of adrenaline liberation. The patient should himself be able to drink the glucose solution for the discontinuation of the hypoglycaemia. Return of hypoglycaemia may in rare cases occur, either in a mild form which the patient himself should be instructed how to deal with, or in a more dramatic form in which intravenous injection of glucose is necessary.

A serious disadvantage of repeated intravenous adrenaline infusions is the irritation of the walls of the infused veins which leads eventually to their occlusion. Further details of the technique of adrenaline infusion have been given elsewhere (Godlowski, 1948a). The contra-indications for this type of treatments are generalized or localized arteriosclerosis, hypertension, and cardiovascular involvement.

To avoid these difficulties an aqueous solution, 0·1 per cent. of adrenaline, has been injected subcutaneously five times daily as a substitute form for the intravenous infusion. The effect of such adrenaline administration was entirely unsatisfactory from the point of view of the therapeutic effect. The explanation of this failure may lie in rapid destruction of the adrenaline, and lack of permanent level of adrenalinaemia, which appears to be essential for the cortical stimulation. The suspension of adrenaline with delayed resorption can fulfil this demand and replace the intravenous infusions. Such form of application has another advantage, that it may be made by the patient himself at home after the preliminary treatment in hospital.

The explanation of the mechanism of the therapeutic action of ACTH and cortisone in rheumatic diseases is not yet clear. There are, however, few points indicating that the suprarenal cortex itself is not primarily involved in the aetiology of the rheumatic affections, since agents stimulating cortical functions act equally as well as the cortisone itself. This means that the suprarenal cortex has not lost its ability to produce hormones in response to the physiological stimulation of ACTH or adrenaline ; positive results, however, are guaranteed if both cortisone or ACTH dosage is very high.

Another fact of great importance, which must not be overlooked in elucidating the mechanism of the curative activity of the ACTH and cortisone, is the appearance of symptoms pathognomonic of hyperadrenalism when the dosage of these hormones is high enough to alleviate the symptomatology of the rheumatic affections ; such signs as obesity, hirsutism, etc., observed in the course of successful

treatment with cortisone or ACTH are characteristic of adrenocortical hyperfunction. In other words, to achieve the desired therapeutic effects in rheumatically affected organs the cortisone concentration must reach a pathological level which leads to pathology of the adrenocortical hyperactivity type in non-affected organs. This result may be interpreted as the lowering of the sensitivity of the tissues rheumatically affected to the physiological concentration of the cortical hormone, whereas the non-affected tissues retained their normal susceptibility to the cortical hormone. The rapid recurrence of the inflammatory symptoms when cortisone or ACTH is withdrawn allows one to postulate that the high doses of these hormones necessary to produce cure have to overpower the hypo- or insensitivity of the affected tissues to the cortisone itself in order to cause a rapid regression of the inflammatory process, but that they do not affect the aetiological agent which precipitated this inflammation. If this theory is correct, the curative activity of the ACTH and cortisone exerts beneficial activity solely on the inflammation which is an integral sign of the rheumatism. The noxious agent lowering the susceptibility of the altered tissues to the physiological concentration of cortical hormones persists in the organism during the time of clinical improvement, since soon after withdrawal of hormonal treatment the full picture of previous intensity of the rheumatic disease rapidly reappears. Thus the instrument of pathogenic activity of the rheumatic noxa, that is, inflammation, is temporarily eliminated.

This explanation being accepted as working theory, it would be of interest to find the answer to two other questions : (1) Which part of cortisone activity may be made responsible for the protective action against inflammation of the organs affected by the rheumatic noxa ? ; (2) Is this anti-inflammatory activity of the adrenocortical hormone specifically directed against inflammation occurring in rheumatic diseases only ?

The conclusive answers to these fundamental questions are beyond the scope of this paper. Certain suggestions, however, based on the previous observations, may be permissible.

Injections of sufficient quantities of ACTH cause in men a significant eosinopenia which is equally well produced by cortisone itself (Thorn and others, 1948). The same eosinophilic drop was observed when adrenaline was administered intravenously in prolonged infusion (Godlowski, 1948a). Another observation indicated that eosinophils possess the transportation ability of the specific antigen (Godlowski, 1948b). There is also the generally known fact that adrenocortical hormones and adrenaline itself produce definite improvements when administered in allergic conditions. (The immediate improvement in allergic reactions caused by adrenaline may also be explained by its action on the capillaries.) Might it then be possible that cortisone, in producing eosinopenia, makes the transport agent for the antigen inavailable and thus temporarily eliminates it from the antigen-antibody reaction ?

There may, however, be another answer to the first question. Cortisone has a potent regulating activity on the electrolite metabolism of tissues (Prunty and others, 1948 ; and others). The quantitative alteration in the potassium and sodium equilibrium is commonly observed in the inflammatory reaction. Significant intracellular retention of sodium salts and water retention in extracellular compartment on the one hand, and substantial elimination of the potassium salts from the cytoplasm on the other, may be the biochemical mechanism of the cortisone activity on the affected tissues. This process may also take place in the eosinophils to such a degree that disturbed balance finds its expression in the physico-chemical alterations of their cytoplasm, with resulting surface-tension changes. In the course of the capillary passage, eosinophils with such surface alterations adhere to the capillary walls and are thus temporarily eliminated from circulation.

The histological features of the inflammation observed in rheumatism do not differ essentially from any other inflammation of an allergic type. The answer to the second question may therefore be that the therapeutic effect of the cortisone on the rheumatic inflammation may be regarded *as a non-specific but very potent factor in regulating the essential mechanism of the inflammation itself but not affecting the aetiology of the disease*. In other words, cortisone acts specifically against inflammation but not against rheumatism.

This theory requires for its support the evidence produced by clinical trials of cortisone in various conditions characterized by inflammatory processes of allergic aetiology.

Summary

1. Stimulation of the adrenal cortex by adrenaline administered intravenously or subcutaneously and by repeated insulin hypoglycaemias has been used for the treatment of rheumatoid arthritis and for non-articular rheumatism.

2. The rationale of this treatment is put forward with tentative explanation of the mechanism of the ACTH and cortisone action in rheumatic affections.

3. A case of advanced rheumatoid arthritis and two cases of non-articular rheumatism which benefited by this treatment are presented.

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Stimulation des glandes surrénales dans le traitement de l'arthrite rhumatismale chronique

Résumé

La stimulation de l'écorce surrénale au moyen de l'adrenaline administrée par la voie intraveineuse ou sous-cutanée et au moyen de l'hypoglycémie insulinique répétée fut employée dans le traitement de l'arthrite rhumatismale et du rhumatisme musculaire aigu. On discute la raison logique de ce traitement. On décrit un cas d'arthrite rhumatismale avancée et deux cas de rhumatisme musculaire aigu qui ont bénéficié de ce traitement.

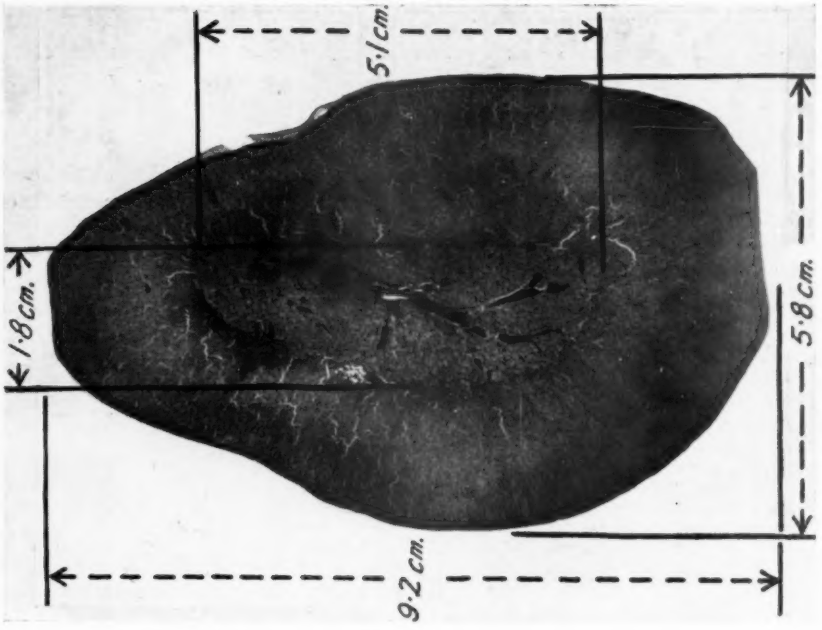

FIG. 2.—Section of a suprarenal gland of a rabbit killed three days after the last attack of insulin hypoglycaemia. Other details as in Fig. 1.

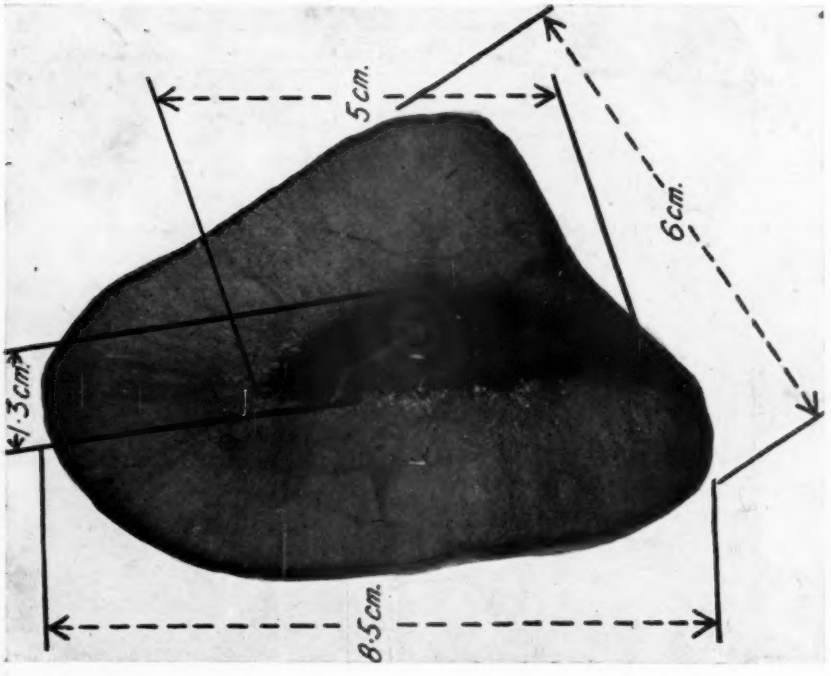

FIG. 1.—Section of a suprarenal gland of an average normal rabbit. Staining, haematoxylin and eosin. Magnification, × 11. Details : Godlowski, 1947.

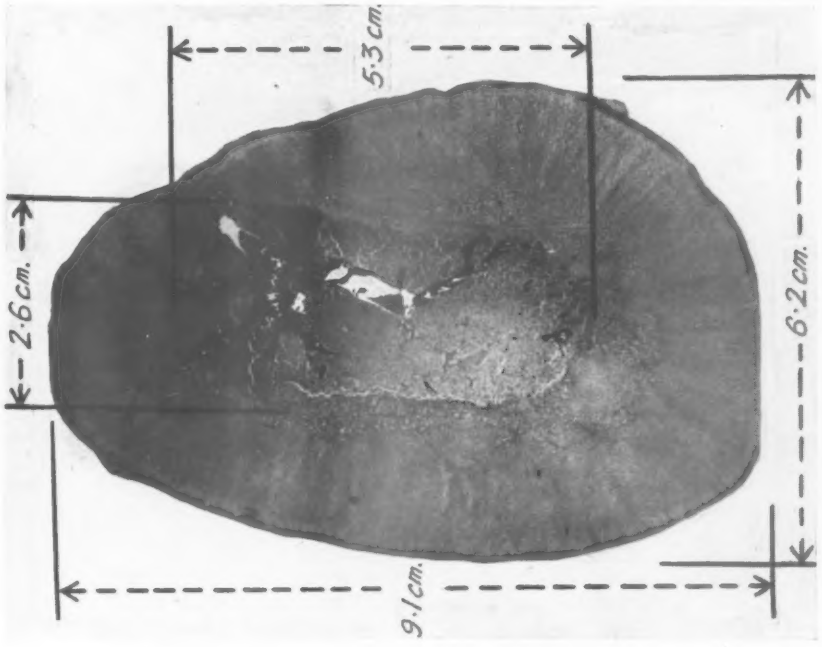

FIG. 4.—Section of a suprarenal gland of a rabbit killed thirty days after the last attack of insulin hypoglycaemia. Other details as in Fig. 1.

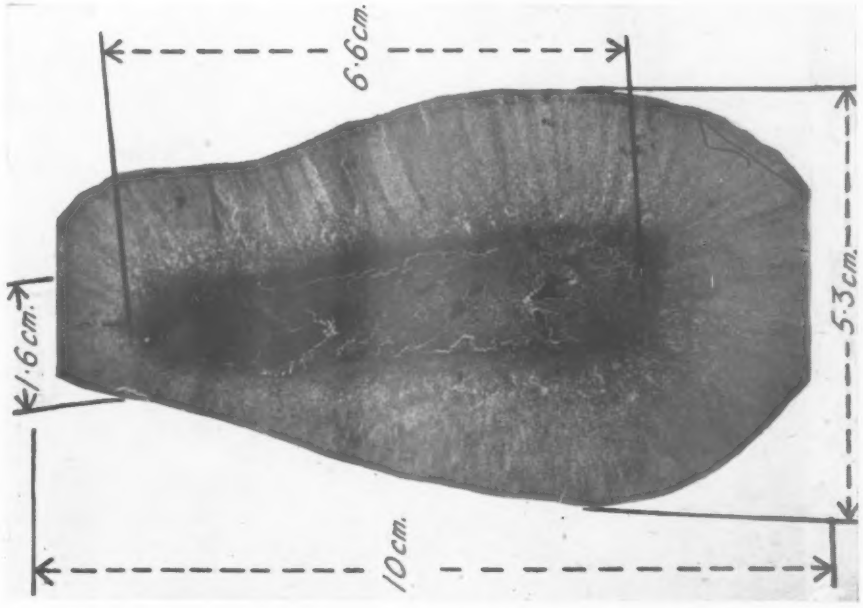

FIG. 3.—Section of a suprarenal gland of a rabbit killed fifteen days after the last attack of insulin glycaemia. Other details as in Fig. 1.

FIG. 5.—Maximal flexion in both wrist joints with grossly restricted movements in the left hand. Gross impairment of finger flexion of the right hand. Condition before treatment.

FIG. 6.—Significant improvement in flexion in the left wrist and right fingers. The remaining impairment in flexion is due to permanent osseous deformity. State after twenty-eight days' treatment.

TREATMENT OF RHEUMATOID ARTHRITIS WITH ADENOSINTRIPHOSPHORIC ACID (ATP)

BY

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In papers published between 1940 and 1945 we reported the results of an investigation on the intermediary metabolism in rheumatoid arthritis, and showed that adenosintriphosphoric acid (ATP) has a beneficial effect on the course of this disease. In the present paper we propose to give a brief review of these investigations and to consider the results in relation to the observations made by Hench and others (1949).

We have found that in some cases of rheumatoid arthritis, vitamin B therapy has a certain, although in many instances rather unsatisfactory, effect, which is sometimes intensified by simultaneous phosphate therapy. On these observations we based our working hypothesis that the cause of rheumatoid arthritis is probably to be found in disturbances of carbohydrate metabolism.

Carbohydrate Metabolism

In order to clarify this question we made quantitative determinations on whole blood of some intermediary products of the metabolism of carbohydrates, chiefly on pyruvic acid and citric acid, with the patient at rest, and also after exertion. At rest the mean value for citric acid, in tests on an empty stomach, was lower in rheumatoid arthritis (1·366 mg. per 100 c.cm.) in about one hundred cases examined than normal (1·835 mg. per 100 c.cm.), and the deviation was statistically significant. For pyruvic acid the mean value (0·909 mg. per 100 c.cm.) was higher than normal (0·835 mg. per 100 c.cm.), but the deviation was not statistically significant. After exertion the values for citric acid in whole blood were lower in rheumatoid arthritis than normally, with statistically significant difference.

Determination of serum iron was done in fifty-two cases of rheumatoid arthritis and showed lower values (0·039 mg. per 100 c.cm.) than normal (0·114 mg. per 100 c.cm.), with statistically significant deviations. On electrophoresis, serum from ten cases of rheumatoid arthritis showed unchanged albumin-globulin ratios with increased content of globulin, particularly γ-globulin.

ATP Therapy

As these examinations seemed to indicate a lowered metabolism of carbohydrates, we considered it justifiable to try a therapy that would stimulate the conversion of carbohydrates. For this purpose we first used muscle adenylic acid, but changed later to ATP. One hundred and forty-four cases of rheumatoid arthritis were treated with ATP. Of these, about 66 per cent. showed marked improvement or recovered completely for longer or shorter periods immediately after the treatment. In about 19·4 per cent., however, the recovery was such that we are not able to state definitely whether it was a result of the ATP treatment. Only 14·6 per cent. showed no apparent response.

After the completion of the treatment with ATP, the blood was examined in the same manner as before the treatment. In those cases where there was clinical improvement, all the values for citric acid, before as well as after exertion, showed a statistically significant rise. In the cases where there was no recovery, on the other hand, there was no elevation of the citric acid values. The values for pyruvic acid showed a tendency to decrease, but the deviation was not statistically significant. The immediate effect of treatment with ATP was a decrease of citric acid and an increase of pyruvic acid. The values for serum iron rose to normal level after treatment with ATP, which was followed by clinical improvement. The albumin-globulin ratio was also normalized, in that the albumin increased and the globulin, particularly the γ-globulin, decreased.

It seems to us reasonable to presume that the deviations from the normal of the values for citric acid and pyruvic acid in the blood in rheumatoid arthritis are evidence of a disturbance, most likely a lowering, of the metabolism of carbohydrates. This presumption is also borne out by the fact that treatment with ATP, which from a biological point of view is of importance mainly in the enzymatic phosphorylation, has a beneficial effect in cases of rheumatoid arthritis, and that the blood values for citric acid and pyruvic acid return to normal

simultaneously. The tests for serum iron, and electrophoresis tests of blood serum, show that there are concurrent disturbances in the conversion of iron and proteins.

Liver Function and Rheumatoid Arthritis

Hench and others have pointed out that intercurrent hepatitis with jaundice in patients who have rheumatoid arthritis often causes a temporary remission of the articular symptoms. This has been verified in our investigations. It is a known fact that in hepatitis there is often a rise in the values for citric acid and serum iron. In rheumatoid arthritis, on the other hand, these values are lower than normal, as shown in the foregoing. In our opinion these facts suggest that there may be a connexion between rheumatoid arthritis and changes in the function of the liver. For this reason we made a close study of the pathological anatomical picture of the liver in this disease. In ninety-three autopsy cases of rheumatoid arthritis fatty changes in the liver were demonstrated in 42 per cent., amyloid degeneration of the liver in 8 per cent., and cirrhosis of the liver in 10·7 per cent. The corresponding figures for an average autopsy material are 2 per cent., 1 per cent., and 3 per cent. respectively. In view of the high incidence of changes of the liver in rheumatoid arthritis, it seems to us very probable that there is some connexion between the two.

The disturbance in the intermediary metabolism of carbohydrates, which in all probability is present in rheumatoid arthritis, may presumably be associated with the appearance of fatty liver, just as fatty liver is a result of diabetes mellitus. In animals there are diseases caused by inadequate conversion of carbohydrates, which regularly involve fatty degeneration of the liver and which respond favourably to ATP. Lehninger in his experiments has shown that the oxidation of fatty acids in the liver requires the presence of ATP. The fatty degeneration of the liver in rheumatoid arthritis would thus be further evidence of the lack of active ATP in the organism.

In 1942, on the basis of these investigations, we wrote as follows:

> "In recent years the opinion that rheumatic diseases are due to disturbances in the metabolism of carbohydrates (Pemberton, Wille, and others) has gained an increasing number of supporters. This concept need not be opposed to other concepts. It lies, so to speak, on a different plane. Toxic changes in the tissues, meteorologic factors, allergic changes in the reaction of the mesenchymal tissue and disturbances in the internal secretion may naturally give rise to or consist in disturbances in the metabolism of carbohydrates. In a great number of rheumatic diseases of various types we have been able to demonstrate disturbances in the metabolism of carbohydrates, and we have also been able to treat these diseases effectively with biogenic substances which have biochemical effects, in that they are in one way or another active in the metabolism of carbohydrates. This seems to be clear evidence in support of the opinion that disturbances in the metabolism of carbohydrates play a decisive part in the appearance of pathological changes in the tissues in these diseases. It may obviously be presumed that in those rheumatic diseases that are affected favourably by ATP the result is due to the fact that those glands of internal secretion which produce enzymes active in the phosphorylation (for example sexual glands, adrenal glands, hypophysis)—as a result of intoxication, physiological or pathological changes—degenerate or atrophy, or that their function is otherwise affected, with consequent disturbances in the metabolism of carbohydrates."

Compound E

These conclusions have been confirmed recently by the important investigations of Hench and others, which show clearly that hormones from the adrenal cortex (Compound E) as well as from the hypophysis (ACTH) induce prompt remission of nearly all symptoms in rheumatoid arthritis. We do not as yet know how the effect of these hormones is accomplished in the organism. Judging from the size of the required doses (100 mg. of Compound E), it is not a matter of actual substitution therapy. Vogt (1944), on the other hand, has demonstrated that the adrenal glands of a 10 kg. dog, which together weigh about 1 mg., in twenty-four hours excrete the same amount of 17-ketosteroids as that present in 17 kg. of adrenal glands. This seems to indicate that the doses given should not be considered as physiologically too large.

A remarkable fact is that those 17-ketosteroids that mainly regulate the conversion of electrolytes have no therapeutic effect in cases of rheumatoid arthritis. Compound E, which influences principally the metabolism of carbohydrates and also of proteins, has hitherto been found to be the only definitely effective agent. Zeller, who at present is studying these problems at the Mayo clinic, has expressed the opinion that Compound E can hardly be effective in any other way than by influencing enzymes, in the first place those enzymes the active group of which is ATP.

Treatment with Compound E would thus stimulate the metabolism of carbohydrates, which would explain the therapeutic effect. The principal cause of rheumatoid arthritis would thus be a reduction in the power to convert carbohydrates, which in its turn is due to functional disturbances

in the adrenal cortex or the hypophysis. It does not seem improbable that the sexual glands would also be involved, partly because rheumatoid arthritis in many cases appears in connexion with the menopause and parturition and is aggravated by menses, partly because the sexual glands produce hormones which are closely related chemically to the hormones of the adrenal cortex. This is in accordance with our comment of 1942.

The satisfactory results that we have obtained from treating rheumatoid arthritis with ATP seem to bear out Zeller's opinion. The explanation of the relatively slow but more constant effect that we have obtained by ATP treatment is perhaps to be found in Vogt's (1949) recent observation that ATP directly stimulates the secretion of the adrenal cortex. It is possible that the increased activity of the adrenal cortex does not appear until after some time; but when it has started it often becomes more permanent.

Our next task will be to investigate whether the conversion of ATP in the organism is disturbed in rheumatoid arthritis, and whether it is affected by the treatment.

Summary

It seems reasonable to presume that the results of our earlier investigations into rheumatoid arthritis show evidence of a disturbance (most likely a lowering) of the metabolism of carbohydrates. This presumption is also borne out by the fact that treatment with ATP, which from a biological point of view is of importance mainly in the enzymatic phosphorylation, has a beneficial effect in cases of rheumatoid arthritis.

It is known that in hepatitis there is often a rise in the values for citric acid and serum iron. In rheumatoid arthritis, on the other hand, these values are lower than normal. There may thus be a connexion between rheumatoid arthritis and changes in the function of the liver. In material from ninety-three autopsy cases of rheumatoid arthritis, fatty changes in the liver were demonstrated in 42 per cent., amyloid degeneration of the liver in 8 per cent., and cirrhosis of the liver in 10·7 per cent.

The important investigations of Hench and others have clearly shown that hormones from the adrenal cortex as well as from the hypophysis induce prompt remission of nearly all symptoms in rheumatoid arthritis. Our treatment with ATP is discussed in view of the investigations of Hench and his co-workers and also in view of other new researches.

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Traitement de l'Arthrite Rhumatismale par l'Acide Adénosintriphosphorique (ATP)

RÉSUMÉ

On se croit justifié de supposer que les résultats de nos investigations antérieures sur l'arthrite rhumatismale apportent des preuves en faveur d'un dérangement (le plus probablement diminution) du métabolisme des hydrates de carbone. Cette supposition se voit également supportée par le fait que le traitement par l'ATP—qui du point de vue biologique, joue un rôle important dans la phosphorylation enzymatique—produit un effet favorable dans l'arthrite rhumatismale.

On sait que dans la hépatite les chiffres de l'acide citrique et du fer dans le sérum se trouvent souvent augmentés. Par contre, dans l'arthrite rhumatismale ces chiffres sont diminués. Il est bien possible qu'il y ait un rapport entre l'arthrite rhumatismale et les altérations de la fonction hépatique. L'examen du matériel d'autopsie de 93 cas d'arthrite rhumatismale a revelé dans le foie la dégénérescence graisseuse dans 42 pour cent, amyloïde dans 8 pour cent, et la cirrhose dans 10·7 pour cent des cas.

Les importantes investigations de Hench et coll. ont montré clairement que les hormones de la substance corticale de la surrénale et ceux de la glande pituitaire font disparaître rapidement presque tous les symptômes de l'arthrite rhumatismale. On discute notre traitement par l'ATP à la lumière des recherches de Hench et coll., et aussi à la lumière des autres investigations récentes.

THE NEUTRAL 17-KETOSTEROIDS IN RHEUMATOID ARTHRITIS AND SPONDYLITIS

BY

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Sjövall (1944), studying the excretion of follicle-stimulating hormone, found that 21 per cent. of female patients under the age of 40 years suffering from rheumatoid arthritis showed evidence of pituitary-ovarian dysfunction.

Davison and others (1947) found no significant alteration in the excretion of 17-ketosteroids in eleven female patients with rheumatoid arthritis, but reported an increased excretion in thirteen male cases of ankylosing spondylitis. In a more recent paper the same authors (1949), dealing with thirty-one male and four female patients suffering from ankylosing spondylitis, found that the high values obtained continued for long periods of time and approached lower levels only when the patients reached a state of exhaustion. Deep *x*-ray therapy seemed to provide a stimulus for increased excretion, followed by a relative decrease although the symptoms and signs of the disease had abated. Patients showing low activity and slow progress of the disease gave normal figures, whereas those with much activity showed increased levels. Most clinical observations suggest that the adrenals are the principal source of urinary 17-ketosteroids. In the male about one third of the total excreted is also derived from the testes (Fraser and others, 1941).

Very few studies of the estimation of the neutral 17-ketosteroids in rheumatoid arthritis have been made, and the work reported here was begun in 1947 as no previous reports could be found in the literature. However, before it was decided to publish this paper the work of Davison and others (1947; 1949) appeared, and in view of the similarity of the results obtained in rheumatoid arthritis it was thought worth while to present it.

The work of Selye (1946) has opened a new field in the understanding of the role played by the adrenals in disease.

In any chronic condition which may or may not have started acutely, the adrenals, after passing through a stage of over-activity, become exhausted, with subsequent reduced excretion of the 17-ketosteroids. Advancing years, the long duration of the disease, and any anaemia present, apart from other conditions such as hypothyroidism, Addison's disease, and hypopituitarism, also tend to diminish the excretion of the steroids in the urine (Fraser and others, 1941). In rheumatoid arthritis, which is now recognized as a systemic disease affecting the mesodermal tissues, it is conceivable that the panarteritis and granulomata described by various authors* in the supporting tissues of muscles, nerves, and synovia may also involve the suprarenals, thus interfering further with their normal functions. The factors governing the excretion of 17-ketosteroids in the urine are multiple, and it was obvious that their isolated estimations would be of value only if correlated with factors which are known to be constant in the diseases under study. In this work an attempt was therefore made to correlate the urinary excretion of the 17-ketosteroids with the age and sex of the patient (Hamburger, 1948), the duration of the disease, the sedimentation rate, and the activity of the disease, using for the last factor an arbitrary scale of 0-8 as an "activity index" by rating the degree of loss of weight, intensity of joint pains, sedimentation rate, and anaemia on a three-point scale (0, 1, and 2 points) for each factor. The activity index thus ranged between a minimum of 0 to a maximum of 8 points.

Material

The total urinary neutral 17-ketosteroids were estimated in 87 patients at the Royal National Hospital for Rheumatic Diseases, Bath. The cases were taken at random and consisted of thirty-six female patients and thirty-one male patients suffering from rheumatoid arthritis. In addition eight cases of ankylosing spondylitis, of which two were females, three cases of Still's disease, and nine other cases

* Curtis and Pollard, 1940; Freund and others, 1942, 1945; Steiner and others, 1946; Gibson and others, 1946; Desmarais and others, 1948.

consisting of fibrositis, gout, and non-specific infective arthritis were also included in the series.

The ages of the female patients with rheumatoid arthritis ranged from 21 to 60 years. The duration of the disease was from six months to 27 years. The activity index varied between 2 and 8. In the thirty-one male patients with rheumatoid arthritis the ages ranged from 23 to 67 years. The duration of the disease was from six months to 27 years, and the activity index varied between 1 and 7. The ages of the six male cases of spondylitis ankylopoietica ranged from 21 to 46 years. The disease had lasted from three to ten years, and the activity index varied between 1 and 8. The two cases of ankylosing spondylitis in the females were 41 and 46 years old. The duration of the disease was six years for both, and the activity indices were respectively 7 and 1.

All the cases of spondylitis had received in the past one or several courses of deep *x*-ray therapy with good results.

The three cases of Still's Disease were 16, 15, and 21 years old, with a duration of 4, 1, and 11 years respectively. Their activity indices were 7, 4, and 6 respectively.

The other cases consisted of seven men and two women. Their ages ranged from 18 to 60 years. The duration was from one to three years and the activity index varied between 0 and 5.

Methods

The determination of the neutral 17-ketosteroids was done by the combined hydrolysis and extraction method of Callow and others (1939) with minor modifications of the technique. The calorimetric estimations were carried out according to Callow (1938) and Zimmermann's (1935; 1936) method, and the colour read in a Spekker photoelectric absorptiometer using an Ilford green filter. The readings were compared with a standard solution prepared from pure crystalline dihydroandrosterone. Blanks were done using absolute alcohol in place of the alcoholic solution. The total neutral 17-ketosteroids was then calculated for 24 hours volume of urine.

Normal values for adult women were taken as 5 to 15 mg. per 24 hours, with a mean of 9 mg. per 24 hours, and normal values for adult males were taken as 8 to 23 mg. per 24 hours with a mean value of 14 mg. per 24 hours. The sedimentation rate and haematocrit estimations were by the method of Collins and others (1939). The corrected suspension stability (C.S.S.) is the percentage volume of red cells after one hour, corrected for any anaemia present, taking a haematocrit reading of 42 per cent. as being normal. A corrected suspension stability of 85 per cent. or more is taken as normal, and a reading below 60 per cent. is considered maximal.

Results

In the thirty-six female patients suffering from rheumatoid arthritis the level of 17-ketosteroids ranged from 1·9 to 21·8 mg. in 24 hours with a mean value of 8·6 mg. Twenty-seven (75 per cent.) of cases fell within the normal range of 5 to 15 mg. in 24 hours. Two cases gave low normal values of respectively 4 mg. and 4·1 mg. Four cases with low values ranging from 1·9 to 3·2 mg. fell within the older age group, with an average age of 49 years. It is interesting to note that they had all reached the menopause. Two cases showed high normal values of 17 and 17·3 mg. One case with a level of 21·8 mg. was 31 years old, with an activity index of 7.

In the thirty-one male patients with rheumatoid arthritis the 17-ketosteroids ranged from 3·7 mg. to 27·4 mg. for 24 hours with a mean value of 12 mg. Twenty-four (77·4 per cent.) cases fell within the normal range of 8 to 23 mg. per 24 hours. Two cases gave low normal values of 6·1 and 6·2 mg. per 24 hours. Four cases with low values ranging from 3·7 to 4·7 mg. fell in the old-age group with an average age of 54·7 years. Only one case, of a boy aged 23 years with an activity index of 2, gave a moderately high value of 27·4 mg.

In the six male cases of ankylosing spondylitis the 17-ketosteroids ranged from 8·4 to 13·2 mg. per 24 hours, with a mean value of 10·2 mg. The two female cases gave values of 6 mg. and 13·6 mg. respectively. The three cases of Still's disease gave values of 8·2 mg., 6·0 mg., and 5·9 mg. respectively.

The other nine miscellaneous cases gave values ranging from 5·7 mg. to 23·2 mg., with a mean value of 13·7 mg. per 24 hours.

Correlation coefficients were calculated between the level of 17-ketosteroids and the age of the patient, the duration of the disease, the haematocrit, the corrected suspension stability, and the activity index, both in male and female patients suffering from rheumatoid arthritis. In the female patients the correlation coefficients at 5 per cent. level of significance, $\simeq 0{\cdot}33$ for 36 pairs, indicated a significant correlation of $-0{\cdot}382$ between the age of the patients and the 17-ketosteroids. The other factors gave no significant correlations. In the males the correlation coefficient at 5 per cent. level of significance, $\simeq 0{\cdot}355$ for 31 pairs, indicated a significant correlation of $-0{\cdot}435$ between the 17-ketosteroids and the age of the patient and also a significant correlation of $-0{\cdot}435$ between the 17-ketosteroids and the activity index. The other factors gave no significant correlation. None of the above were significant at 1 per cent. level. No attempt at calculating a multiple or a partial correlation coefficient has been made.

Discussion

The excretion of the 17-ketosteroids in rheumatoid arthritis was found to fall within normal limits

in 76·1 per cent. of all cases. The significant correlation between the age of the patients and the 17-ketosteroids in both male and female patients is also true for normal individuals. No satisfactory explanation could be found for the lack of correlation in the female cases between the 17-ketosteroids and activity index and the presence of a significant correlation in the males between these factors.

The eight cases of ankylosing spondylitis had all received one or several courses of deep *x*-ray therapy before the estimations were done. Comparing the results obtained with the findings of Davison and others (1947; 1949), mean values of 10·2 for males and values of 6 mg. and 13·6 mg. for the two female cases are low.

The values found for the three cases of Still's disease fell within normal range for the ages of the patients. The other nine miscellaneous cases gave values which were within the normal range, with a mean value of 13·7 mg.

From the above findings the estimation of 17-ketosteroids in rheumatoid arthritis is found to be of very little clinical value. If the urinary excretion of 17-ketosteroids is taken as a reflection of the androgenic function of the adrenals, we find that this factor is not materially affected in this disease. It would, however, be of interest to study the excretion of glycogenic corticoids in parallel with the excretion of 17-ketosteroids, which would give a more detailed picture of the activity of two different aspects of adrenal function in the same patient.

Summary

The excretion of neutral urinary 17-ketosteroids in eighty-seven cases of rheumatic conditions were estimated by the Callow-Zimmermann method. In thirty-six female and thirty-one male patients suffering from rheumatoid arthritis, 75 per cent. and 77·4 per cent. of cases respectively, fell within normal limits of excretion. A significant correlation was found between the 17-ketosteroids and the age of the patients, both in male and female cases. In the males a significant correlation was also found between the activity index and the 17-ketosteroids, but none in the female patients. No explanation for this discrepancy could be put forward. From these findings the estimation of 17-ketosteroids in rheumatoid arthritis was found to be of little clinical value.

The mean value for eight cases of ankylosing spondylitis was found to be low when compared with the findings of Davison and others (1947; 1949). All the cases had received deep *x*-ray therapy. Nine other miscellaneous cases, and three cases of Still's disease, were all within normal limits.

I wish to express my thanks to the physicians of the Royal National Hospital for Rheumatic Diseases, Bath, for giving me access to the cases under their care. I am also indebted to Dr. M. Reiss at the Endocrinological Research Institute, Fishponds, Bristol, for his valuable technical advice regarding the method of estimation of the 17-ketosteroids in the urine. I am grateful to Mr. J. A. Heady, Statistician, St. Bartholomew's Hospital, London, for working out the statistical correlations expressed in this work.

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Les 17-Cétostéroïdes neutres dans l'Arthrite Rhumatismale et la Spondylite.

Résumé

L'excrétion urinaire des 17-cétostéroïdes neutres fut déterminée dans 87 cas d'affection rhumatismale par la méthode de Callow-Zimmermann. Chez 36 femmes et 31 hommes atteints d'arthrite rhumatismale cette excrétion se trouvait endéans les limites normales dans 75 pour cent et 77·4 pour cent de cas respectivement. On a trouvé un rapport significatif, chez les hommes et chez les femmes, entre les 17-cétostéroïdes et l'âge des malades. De même, on a observé un rapport significatif entre l'indice d'activité et les 17-cétostéroïdes chez les hommes, mais pas chez les femmes.

On a trouvé que le chiffre moyen, par rapport aux résultats obtenus par Davison et coll. était bas dans huit cas de spondylite ankylosante. Tous les cas furent traités par des rayons *x* profonds. Dans neuf cas divers et dans trois cas de maladie de Still les chiffres se trouvaient endéans les limites normales.

DIFFERENTIAL SHEEP-CELL AGGLUTINATION TEST IN RHEUMATOID ARTHRITIS*

BY

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In March, 1948, Rose and others described a test for rheumatoid arthritis which depended on the ability of serum from patients with rheumatoid arthritis to agglutinate " sensitized " sheep erythrocytes in much higher titre than normal sheep erythrocytes. The authors reported results in 110 patients, of whom 27 had active rheumatoid arthritis and 16 inactive rheumatoid arthritis, 3 Still's disease, and 5 Marie-Strümpell arthritis : 59 were non-rheumatic controls. Only the patients with rheumatoid arthritis and related diseases showed an elevation of the agglutination titre for " sensitized " sheep cells. The authors reported that the active fraction was found in the beta gamma globulin fraction of electrophoretically separated serum.

Sulkin and others (1948) reported on 149 patients including 35 with active rheumatoid arthritis, 1 with Still's disease, and 7 with Marie-Strümpell spondylitis. Forty-six per cent. of these patients and none of the controls had a raised titre for agglutinins of " sensitized " sheep cells. The authors correlate the presence of a raised titre with greater severity and increased duration of the disease.

Jawetz and Hook (1949) reported the results of this test in 161 patients of whom 78 had rheumatoid arthritis. In this study 65 per cent. of the patients with markedly active rheumatoid arthritis and 13·5 per cent. of the group classified as mildly or moderately active had an elevation of the agglutination titre for " sensitized " sheep erythrocytes ; none of the inactive group had a raised titre. In the controls there were two patients, one with hepatitis and one with ankylosing spondylitis, who had a raised titre for the " sensitized " sheep cells.

Our report presents the results of the sheep-cell agglutination test performed on sera of 164 patients and 13 normal adult males. The cases studied included rheumatoid arthritis, and, as controls, other rheumatic disorders and non-rheumatic diseases.

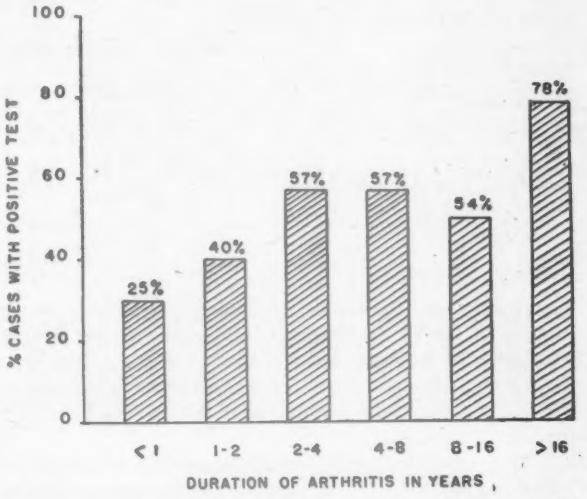

FIGURE.—Relation of incidence of positive tests to the duration of rheumatoid arthritis.

Methods and Materials

In these tests commercially preserved sheep erythrocytes and anti-sheep rabbit serum preserved with 50 per cent. glycerine were used.

As a preliminary test the rabbit serum was titrated against a 1 per cent. suspension of normal preserved sheep erythrocytes. Dilutions of the serum were made from 1 : 100 to 1 : 1,000 in saline in 0·5 ml. volume. To each of the ten tubes was added 0·5 ml. of a 1 per cent. sheep erythrocyte suspension in saline. The tubes were shaken, incubated for one hour at 37° C., placed in the refrigerator overnight, and read the next morning for agglutination. Most of the lots of anti-sheep serum agglutinated the sheep erythrocytes to a final dilution of 1 : 600 or 1 : 800. In " sensitizing " the sheep cells for the agglutination test, the dilution of the rabbit serum used was twice that in the last tube which gave a 1+ agglutination in the preliminary titration described above. At least ten minutes was allowed to elapse

* This investigation was aided by a grant from the Masonic Foundation for Medical Research and Human Welfare.

between the addition of the anti-sheep rabbit serum to the sheep cells and the addition of the sensitized sheep cells to the patient's serum.

The sera of patients were obtained from freshly drawn venous blood and inactivated by heating at 56° C. for thirty minutes. Two twelve-tube series of serial twofold dilutions in 0·5 ml. volumes were prepared. To the first series of tubes 0·5 ml. of a 1 per cent. suspension of sensitized sheep erythrocytes, prepared in the manner described above, was added, and to the second series of tubes 0·5 ml. of a 1 per cent. suspension of normal sheep erythrocytes. Thus the final dilution of reagents in the first tube of the first series was: patient's serum, 1 : 4; sheep cells, 0·5 per cent. suspension; anti-sheep rabbit serum, 1 : 3,200 if the titre in the preliminary titration of sheep cells against rabbit serum was 1 : 800.

The tubes were shaken and incubated at 37° C. for one hour, then placed in a refrigerator overnight, and read the next morning for agglutination. A typical series of readings was as follows:

	Dilution of Patient's Serum								
Rheumatoid arthritis ..	1:4	1:8	1:16	1:32	1:64	..	1:2,048	1:4,096	1:8,192
Normal sheep erythrocytes	4+	4+	4+	1+	0	..	0	0	0
Sensitized sheep erythrocytes	4+	4+	4+	4+	4+	..	3+	1+	0
Osteo-arthritis									
Normal sheep erythrocytes	4+	4+	4+	1+	0	..	0		
Sensitized sheep erythrocytes	4+	4+	4+	4+	1+	..	0		

The results of the test are expressed as the quotient of titre of the "sensitized" sheep cells divided by the titre of the normal sheep cells. This is called the differential titre. Thus in the first example given above the differential titre would be 4,096 divided by 32, or 128.

The haemolytic streptococcus agglutination titration was done against Griffith types 1 and 19 and Lancefield type 38 of group A haemolytic streptococci.* Stock cultures were kept in neopeptone rabbit blood broth, and cultures for use in the test were incubated overnight (fifteen hours) in bactopeptone broth. Living cultures were used in the test, and these were incubated at 55° C. for one hour, and read the following morning for agglutination after refrigeration overnight. A positive test for the purposes of this paper consists of a 2+ agglutination against all three types at a 1 : 20 dilution and a 2+ agglutination of 1 : 160 against at least one of the types.†

TABLE 1

RESULTS OF TESTS FOR SHEEP CELL AGGLUTININS IN SERA OF 83 PATIENTS USED AS CONTROLS†

Differential titre ..	1	2	4	8	16
Number of cases ..	9	40	25	8	1

† The control cases included:

Normal adult males	13
Degenerative arthritis (osteo-arthritis)	16
Acute rheumatic fever	9
Rheumatic heart disease (inactive)	4
Gout	4
Reflex dystrophy of extremities	3
Subdeltoid bursitis	3
Staphylococcic arthritis	1
Subacute bacterial endocarditis	3
Acute glomerulonephritis	6
Traumatic arthritis	1
Miscellaneous medical conditions	20
Total	83

* These strains were given to us by Mrs. Miriam Olmstead Lipman of the Presbyterian Hospital, New York City.

TABLE 2

RESULTS OF TESTS FOR SHEEP-CELL AGGLUTINATIONS IN SERA OF 62 PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

Differential titre	1	2	4	8	16	32	64	128	256	512 or higher
Number of cases	4	7	7	10	8	8	7	5	3	3

TABLE 3

RESULTS OF TESTS FOR AGGLUTININS FOR GROUP A HAEMOLYTIC STREPTOCOCCI AND FOR SENSITIZED SHEEP CELLS IN SERA OF 51 PATIENTS WITH RHEUMATOID ARTHRITIS

H.S. Agglutinins	Sensitized Sheep Cells	%
Positive	Positive	39·2
Positive	Negative	13·7
Negative	Positive	15·6
Negative	Negative	31·4

Results

The distribution of the differential titres of the 83 control patients is shown in Table 1. With the exception of one patient, who had subacute bacterial endocarditis and active rheumatic carditis, and whose differential titre was 16, all sera gave a titre of 8 or less. In this report, therefore, a differential titre of 16 or higher is considered a positive test.

Sixty-two patients with active rheumatoid arthritis are included in this series. The distribution of their differential titres is shown in Table 2. The term "active" as used in this study implies signs of an active process in a joint as indicated by swelling, warmth, and tenderness. Of these patients, 34, or 55 per cent., had a differential titre of 16 or higher, and 28 patients, or 45 per cent., had a titre of 8 or less. The haemolytic streptococcus agglutination test was done on the sera of 51 of these 62 patients. The relation of the results of one test to the other is shown in Table 3. It will be noted that 54·8 per cent. had a positive sheep-cell agglutination test, while 52·9 per cent. had a positive haemolytic streptococcus agglutination titre. In 39·2 per cent. both tests were positive; in 15·6 per cent. the sheep-cell agglutination test was

† For further information concerning this test, consult the paper by Nicholls and Stainsby (1931), Dawson and others (1932), McEwen and others (1936), and Boots and others (1949, in the press).

positive and the haemolytic streptococcus agglutination test negative ; in 13·7 per cent. the sheep-cell agglutination test was negative and the haemolytic streptococcus agglutination test positive. In 31·4 per cent both tests were negative.

The relation of the duration of disease to the incidence of a positive sheep-cell agglutination test is shown in the Figure. There is a rising incidence of positive tests from 25 per cent. of cases of less than one year's duration to 78 per cent. of cases with a duration of sixteen years or longer.

In this group of patients with active rheumatoid arthritis, there were 3 with a normal erythrocyte sedimentation rate and a positive sheep erythrocyte agglutination test ; while conversely the vast majority of patients with differential titres in the normal range had an accelerated erythrocyte sedimentation rate. Thus no correlation can be drawn between these two tests.

Twenty patients in this series had inactive rheumatoid arthritis. Of this group, 6, or 30 per cent., had a differential titre of 16 or higher. In 17 of the 20 patients both the haemolytic streptococcus agglutination test and the sheep-cell agglutination test were done. Five of these 17 patients, or 29 per cent., had a positive sheep-cell agglutination test, while 7, or 41 per cent., had a positive haemolytic streptococcus agglutination test. All the five patients with a positive sheep-cell agglutination titre had a positive haemolytic streptococcus agglutination titre.

In the group of patients with rheumatoid arthritis there were 13 with subcutaneous nodules. Of these 13 patients, 7, or 54 per cent., had a differential titre of 16 or higher ; of the 12 patients in this group whose sera were analysed for haemolytic streptococcus agglutinins, 9, or 75 per cent., gave a positive test.

There were 9 cases of Marie-Strümpell spondylitis. Two patients, both of whom had involvement of at least one peripheral joint, had titres of 16. In the remaining 7 patients the titres were 8 or less. There were two cases of psoriatic arthritis and one case of Felty's syndrome ; all three had a differential titre of 8 or less.

Summary

The sheep erythrocyte agglutination test was found to be positive in 55 per cent. of sixty-two patients with active rheumatoid arthritis and in 30 per cent. of twenty patients with inactive rheumatoid arthritis. There was a close but not an exact correlation with the haemolytic streptococcus agglutination titres. The incidence of elevated differential titres increased as the duration of the disease increased. There appeared to be no significant relationship between titre and the presence of subcutaneous nodules. In the non-rheumatoid control group of 83 sera, only one had a differential titre of 16. All the others were below this value.

We wish to acknowledge the technical assistance of Mrs. Clarice Illes and Miss Lotte Weilheimer in performing the serologic tests.

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Epreuve d'Agglutination Différentielle des Erythrocytes du Mouton dans l'Arthrite Rhumatismale

RÉSUMÉ

L'épreuve d'agglutination des érythrocytes du mouton fut positive dans 55 pour cent des 62 cas d'arthrite rhumatismale active et dans 30 pour cent des 20 cas d'arthrite rhumatismale inactive. Il y avait un rapport étroit mais pas exact aux titres d'agglutination causés par le streptocoque hémolytique. La fréquence des titres différentiels élevés augmentait au fur et à mesure que la maladie se prolongeait. Il semble qu'il n'y avait aucun rapport significatif entre les titres et la présence des nodules sous-cutanés. Dans le groupe témoin non-rhumatismal de 82 sérums, un seulement avait le titre différentiel de 16 ; chez tous les autres celui-ci était inférieur.

THE SEVENTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

In 1940 it had been planned to hold a Congress of the Ligue Internationale contre le Rhumatisme in America, but this had to be cancelled because of the war. In 1945 there were rumours of an important Congress to be organized in the U.S.A. in 1948 or 1949, and by 1946 the late Professor Ralph Pemberton was hard at work making preparations for this event. His unceasing efforts on behalf of this Congress contributed largely to his death. In January, 1947, the first official invitation was circulated by Dr. Richard Freyberg, on behalf of the American Rheumatic Association, asking members of the Ligue to be their guests at this Seventh International Congress to be held in America in 1949, and in 1948 Dr. Philip Hench himself did a tour of this country and the continent, collecting views and disseminating information about the Congress.

These tremendous preparations augured well, but, those of us who have attended a number of such meetings elsewhere, had our greatest expectations surpassed by the success of this one. The American hospitality and forethought came well up to its famed standard; the delegation from overseas exceeded all estimates, twenty-six different countries being represented, the list being topped by Great Britain and Canada with twenty-nine and twenty-eight delegates respectively.

The high spot of the Congress was, however, the quality of the hundred papers presented. They covered the whole field of rheumatology but especially stressed the fundamentals of morbid histology, histochemistry, and above all endocrinology. The first international presentation of the work of Hench, Kendall, Slocumb, and Polley of the Mayo Clinic, of Bauer and Thorn of Boston, and Woolfson of Chicago on this latter aspect was of such interest that, to quote Hench in lighter vein, the discussion took the lines of "rheumocrinology".

After the main meeting at New York, a post-convention tour was organized to take in the American Medical Association meeting at Atlantic City, and research centres and hospitals at Philadelphia, Boston, Buffalo, Chicago, Detroit, the Mayo Clinic, Washington, Toronto, and Montreal, and here ample opportunity was afforded to see the background of much of the work discussed at New York and in particular the treatment of rheumatic cases with Cortisone and ACTH.

The impression gained by many of us was of the vast strides recently made to put rheumatology on a sound academic footing and of the vast sums being spent, especially in America, on both research and treatment of the rheumatic diseases. The Cinderella of medicine had met her Prince Charming.

This did not, however, apply to America only, as excellent work was being done at numerous centres on the Continent, though, perhaps with the exception of Denmark and Sweden, the economic difficulties were hampering their efforts to some extent.

During the course of the Conference, and during the succeeding days, many useful and important discussions took place on the endocrinological and histological aspects of rheumatism. In addition to an elaboration of the work already published on the benefit of the corticotrophic hormone of the pituitary and of Compound E on the collagen group of diseases (rheumatoid arthritis, spondylitis, rheumatic fever, dermatomyositis, erythema nodosum and lupus erythematosus generalizatia), interesting data were forthcoming on their effect on gout, and also on the control of a hereditary tendency to hyperuricaemia by an abnormal cortical androgen in this disease.

The morbid histology usually seen in rheumatoid disease was generally considered to be nonspecific but discoverable more commonly and more widely in this disease than in any other condition.

New evidence was produced on hereditary factors in rheumatoid arthritis, spondylitis, and gout, but the old dispute on the relationship between rheumatoid disease and ankylosing spondylitis remained undecided. In the practical sphere the value of pre- and postoperative treatment in orthopaedics, and especially in Smith-Petersen's cup arthroplasty, was strikingly demonstrated.

Short summaries of twenty-eight of the papers given in New York are included in this number; they form a résumé of some of the important work discussed, and may act as an easy reference in future years, when the Proceedings of the Congress, shortly to be published, will be available for consultation of the papers in full.

We are indebted to Messrs. W. B. Saunders and

Co., of Philadelphia, for permission to publish the summaries of the Congress. Many of these papers will be published in full in the Proceedings.

A few papers, for instance one from the Mayo Clinic on Compound E, one by Forestier on copper, and those from Bath on the histology of rheumatoid disease, have already appeared in the Annals in full and are therefore not included among the summaries.

In conclusion we cannot do more than wish the European and Pan-American Congresses of 1951, to be held respectively in Spain and the U.S.A., and the Joint International Congress of 1953 arranged for Switzerland, the same measure of success as this Seventh Meeting recently held in New York.

The Histophysiology of the Connective Tissues

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The four primary tissues of the body represent structural specializations for the performance of certain functions. Connective tissue is specialized to play a supporting and nutritive role under conditions of health, and a defensive one under conditions of infection. To provide proper support in the body requires that connective tissues contain a high proportion of intercellular substances, for these non-living materials are much stronger than living cells.

The nutritive role of connective tissue is determined by the fact that the blood and lymph vessels of the body are all confined to it. Since most cells do not abut on capillaries they must be nourished from the connective tissue that separates them from capillaries. This is usually explained by postulating that connective tissue so disposed, is bathed in tissue fluid that emerges from capillaries as a dialysate of blood plasma and is returned to the circulatory system by both the blood and lymph capillaries of connective tissue.

In playing a defensive role connective tissue serves as the "arena of inflammation". In addition to vascular and specific cellular activities associated with the inflammatory process the intercellular substances of connective tissue may act as a barrier to the spread of infection.

Morphologically two main types of intercellular substances can be identified in connective tissue: (1) a formed type (reticular, collagenic, and elastic fibres), and (2) an amorphous type (ground and cement substances—mucopolysaccharides). Representatives of both main types are present in most kinds of connective tissue but their proportions are different in the different subtypes of connective tissue.

A comparison of the microscopic structure of, and mechanism for nutrition in (1) mesenchyme, (2) cartilage, (3) bone, and (4) synovial membranes and joint capsules, shows that the tissue fluid concept cannot fully account for nutrition in and through all types of connective tissue. The amorphous intercellular substances appear to be specialized for permitting nutritive diffusion phenomena to operate between capillaries and cells. The formed types of intercellular substances on the other hand are specialized chiefly for support.

Evidence obtained from the study of normal development and repair phenomena suggests that the degree to which fibroblasts are differentiated is related to whether they produce amorphous or formed types of intercellular substance.

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The Pathological Distinction between Osteo-Arthritis and Osteophytosis of the Spine

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Osteo-arthritis is the name for a condition which can only affect synovial (diarthrodial) joints. It is a sequence of morbid changes originating in destruction or degeneration of articular hyaline cartilage. Marginal hyperplasia of bone is only one of its later manifestations, and its earliest stages, when cartilage alone is principally affected, are not detectable either radiologically or by the examination of macerated anatomical specimens. The condition affects groups of, or isolated synovial joints of the vertebral column (apophysial and costo-vertebral), and is not necessarily associated with marginal lipping of the vertebral bodies. The latter condition (osteophytosis, or spondylosis deformans) is a consequence of collapse, degeneration, or distortion of one or more intervertebral disks, and the diarthroses between the corresponding segments of the spine may be normal. As long ago as 1897 Benecke related marginal lipping with disorder of the intervertebral disks, a view also held by Schmorl.

The mode of origin of osteophytes of the vertebral bodies has been studied by dissection and histological preparations. Osteophytes cannot form so long as the nucleus pulposus is intact and turgid and the vertebral bodies are normally separated. Collapse of the disk leads to slight forward tilting of the vertebrae and the forward extrusion of what plastic disk substance remains. The periosteum is stripped off the vertebral body on either side of this extruded disk substance, and the osteophytes subsequently develop in and take the form of the area of periosteal elevation. The new bone is typical of reactive bone formed beneath periosteum, and is at first more or less compact. The anterior common ligament prevents the extrusion of disk substance in the mid-line, and this explains the usual absence of osteophytes in this situation. Osteophytes are produced by a similar mechanism in the concavities of a scoliosis. The apophysial joints corresponding to grossly lipped vertebral bodies have been examined histologically and have often shown either healthy or slightly atrophic cartilage but no osteo-arthritis.

Distinction between osteo-arthritis and osteophytosis of the spine may help to clarify the clinical analysis of a difficult group of painful diseases of the spine. The

recognition of an osteo-arthritis of the posterior intervertebral joints occurring independently of radiological evidence of osteophytosis may prove of importance in this connexion.

Diagnosis of Osteo-Arthritis

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The criteria for making a diagnosis of osteo-arthritis vary, and there is much disagreement among doctors as to what symptoms may be attributed to this disease, especially where compensation is involved. The term osteo-arthritis should represent a distinct clinical disease with appropriate symptomatology, not simply a radiological diagnosis. It is suggested that the confusion would be resolved by adherence to a clear definition setting up certain requirements. Localized symptoms of pain and perhaps limitation of motion following a benign and remittent course are appropriate to the disease. Radiographs should confirm pathological alteration at the site. The exact aetiology remains undetermined. These criteria would eliminate those patients with pre-symptomatic *x*-ray changes, those demonstrating physiologic ageing of the joints, and those with hypertrophic changes secondary to a known cause. The diagnosis would be reserved for those patients demonstrating symptomatic and pathologic idiopathic degenerative joint disease. Since the process is recognized as a local tissue change, only the one or few proven joints should be mentioned in a diagnosis. The term "generalized" osteo-arthritis is inacceptable.

The Histopathology of the Neuromuscular System in Rheumatoid Arthritis

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Peripheral nerves or muscles or both from eighty cases of rheumatoid arthritis were histologically examined. Thirty were biopsies of muscle only. In addition the spinal cord was examined in most of the autopsy cases, and in some instances the sympathetic ganglia were also studied.

It was found that small paravascular foci of round cells were present in the interstitial tissue of the nerves and muscles. These foci were usually in the perineurium or perimysium, but were sometimes found in other sheaths as well. The sympathetic chain was similarly affected by cellular infiltrations, not only along the course of the fibres but also within the capsule of the ganglia. About 75 per cent. of the nerves and 65 per cent. of the muscles had these cellular accumulations. Foci were found in the muscles whether blocks were taken from extensors or flexors, from the belly or near the tendon, from close to or far from an involved joint, from atrophied or healthy muscle. Lesions were also widely distributed in nerves, whether motor, sensory or mixed. There was not much relationship between the presence of cellular accumulations on the one hand, and clinical activity of the disease, the age of the patient, and the duration of the disease on the other.

In addition there were in some cases slight alterations in the myelin sheath and axones of the peripheral nerves, with retrograde degeneration of the anterior horn cells of the spinal cord. These anterior horn cell changes were greater than the ordinary changes due to advancing age.

After these nodular foci of round cells had been compared with those found in other diseases of the connective-tissue group, such as lupus erythematosus disseminatus, dermatomyositis, and rheumatic heart disease, it was concluded that no distinguishing diagnostic differences could be relied upon because the appearances in the various diseases were often similar.

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The Peripheral Genesis of Pain

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There are several factors involved in the peripheral production of pain in disease.

In some forms of cutaneous hyperalgesia (erythralgia) warming the part in the range 30° to 45° C. (86° to 115° F.) causes spontaneous skin pain, while with deep hyperalgesia cooling the part in the range 30° to 15° C. (86° to 59° F.) causes spontaneous deep pain. These temperature effects are most easily demonstrated with the circulation occluded and are, therefore, due to the temperature change as such and not to secondary changes of circulation.

The effect of arterial occlusion and venous engorgement has been studied in a variety of painful conditions. At least three patterns of response occur: (a) no effect, found in painful conditions due to morphological changes in the pain receptors and fibres and also in some forms of arthritis; (b) dramatic increase of pain during arterial occlusion, found in abscesses and operation wounds and in some other inflammatory conditions; (c) increase of pain with venous congestion, often combined with a modified increase during arterial occlusion, found in a variety of inflammatory post-traumatic and arthritic conditions.

Various chemical solutions produce different results when injected into the deep tissues. Thus osmotic changes (hypertonic solution) cause a short wave of spontaneous pain only. Alterations of *p*H, particularly acids, cause immediate pain and prolonged hyperalgesia. Alterations of the concentration of particular ions cause various responses; thus KCl causes immediate pain and hyperalgesia, while $CaCl_2$ causes no immediate pain but delayed long lasting hyperalgesia.

Hyperalgesia to mechanical, thermal, and possibly chemical stimuli is an important factor in the production of pain, but there are probably many different mechanisms involved in the production of pain in disease. In conditions which give an increase of pain during arterial occlusion, such as the inflammatory and post-traumatic

states, measures designed to increase the local circulation relieve pain, but when the circulatory tests are negative as in painful states due to morphological changes in the nerves, and in most rheumatic conditions, increasing the local circulation is of little value, though some temporary relief may be obtained from warmth through the effect of temperature on deep pain. More accurate knowledge of the mechanism involved in the peripheral genesis of pain is required if we are to treat pain intelligently by medical, surgical, or physiotherapeutic procedures.

Diseases Arising from Overstrain and Wear and Tear on the Muscles of the Skeletal System, often concealed Behind the Diagnosis of Neurosis and Rheumatism

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Emotional or affective pain occurs because emotions normally increase pain and feeling of fatigue and induce muscular tension, which in itself may call forth pain in tender muscles, tendon attachments, and joints. Anxiety tension finds expression mainly in a fixation of the thorax in the inspiration position, with drawn-up shoulders. The best treatment for neuroses has proved to be relaxation gymnastics, to teach the patient to relax during work and to release the fixed mechanism of respiration. By such daily gymnastic exercises, and training in the proper manner of working with least possible tension, it has been found possible practically to eradicate functional diseases in the musculo-skeletal system as a cause of industrial absenteeism, whereas in 1944, 25 per cent. of the absenteeism was due to over-straining the neck and arms.

The Effect of Δ-5-Pregnenolone on Urinary 17-Ketosteroid Excretion and Symptomatology of Ankylosing Spondylarthritis; a Preliminary Report

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Increased urinary excretion of 17-ketosteroids has been demonstrated in ankylosing spondylarthritis (Marie-Strümpell disease). It is observed in both male and female patients, and is present in early cases with little demonstrable joint change as well as in those patients who have had the disease for many years and show the typical findings of the advanced case.

Δ-5-Pregnenolone is a steroid having several actions not characteristic of other steroids. Its chemical composition makes it a logical process material to act as a precursor of many active steroids. When normal individuals are subjected to acute stress and fatigue, adrenal cortical activity is accelerated and increased rates of 17-ketosteroid excretion are observed. Pregnenolone administered under such conditions lowers the 17-ketosteroid excretion, improves performance, and combats fatigue. This steroid has not to our knowledge been used in disease states. Its general properties, freedom from toxicity, and ability to lower urinary 17-ketosteroid excretion and to combat fatigue suggested to one of us possible value in spondylarthritis.

Δ-5-Pregnenolone acetate in vegetable oil was administered by intramuscular injection in daily dosage of 50 to 150 mg. to patients with active spondylarthritis. Urinary 17-ketosteroid excretion was studied before and during the course of administration of pregnenolone.

Total ketosteroids were measured by extraction of hydrolysed urine with carbon tetrachloride and application of the Zimmermann colour reaction.

Pregnenolone reduced the excretion of 17-ketosteroids in the urine of these patients to normal levels. Accompanying the reduction of 17-ketosteroids, there is striking relief of symptoms and objective signs of the disease. When placebo injection is substituted for the pregnenolone, the ketosteroid excretion increases and the patient regresses. Re-institution of treatment again reduces urinary 17-ketosteroid output, this being accompanied by relief of symptoms. Pregnenolone therapy does not prevent the usual rise in ketosteroid output which results from radiography.

The striking clinical improvement which accompanies the reduction in ketosteroid excretion suggests relationship between the ketosteroid excretion and clinical findings, though not necessarily a causal relationship.

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Synthetic Oestrogens in the Treatment of Ankylosing Spondylitis

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Of twenty-three men with ankylosing spondylitis treated with synthetic oestrogens, thirteen obtained definite and lasting improvement in flexibility of the spine. Diethylstilboestrol was usually employed, sometimes by mouth but more often parenterally to diminish gastro-intestinal disturbances. Preliminary test-treatment with 20 mg. daily intramuscularly is carried out for two weeks. If this is well tolerated and followed by improvement, implantation of 200 to 300 mg. pellets is performed, renewed in six to twelve months. Hexoestrol and dienoestrol, used in a few cases, are much less active than stilboestrol. At present the authors are frequently using doisynolic acid, which is also less active than stilboestrol, but better tolerated.

Except for intolerance to the drug, untoward effects of treatment consist of sexual impotence and painful swelling of the breasts. When these sexual manifestations do not occur, generally no therapeutic effect is obtained. Most patients readily accept these inconveniences, happy to be relieved of pain and to feel their spines becoming more supple. In three cases oestrogen therapy was followed by aggravation of symptoms; in one of these parenteral testosterone resulted in marked improvement.

The sedimentation rate usually decreases after oestrogen therapy, but similar lowering of the sedimentation rate has been observed after oestrogen

administration, independent of any action on an inflammatory process.

The Synovial Membrane in Osteo-Arthritis

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There are many changes found in the synovial membranes in the cases of osteo-arthritis; there is no consistently characteristic type of membrane. Fibrosis, perivascular fibrosis, vascular thickening, haemorrhage, round-cell infiltration and hyalinization, all are found; but none in a high enough percentage of cases to make us feel that the synovial reaction is the primary reaction in cases of osteo-arthritis. An attempt has been made to correlate the changes found in the membranes with those found clinically, but the very fact that no characteristic picture is found makes us believe that the synovial changes are secondary to other changes in the joint degeneration characteristic of osteo-arthritis.

The Range of Pathological Reactions which can be Displayed by Human Synovial Tissues

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Observations based on histological study of 250 synovial membranes have been collated under heads: (1) changes in synovial cells, (2) vascular and exudative phenomena, (3) leucocytic reaction.

(1) Synovial tissues are mesenchymal and display many of the same fundamental reactions as simple connective tissues elsewhere, e.g. atrophy, hyperplasia, degenerations and mutations. Particular properties of synovial cells are the production of extra-cellular mucin, histiocyte differentiation, and the ability to form endothelial-like surfaces. These properties can occasionally be shown by extra-articular connective tissues, but the study of synovial neoplasms suggests that they may be inherent qualities of joint tissues.

(2) The rich capillary vasculature of synovial membrane is only revealed in hyperaemia. The loose-textured tissue and the synovial sac are easily and quickly distended by transudate or exudate. Vascular and exudative phenomena seemingly develop out of proportion to the severity of the inflammatory stimulus and are rarely localized to one part of the membrane.

(3) Normal synovial tissues contain very few leucocytes. Light perivascular lymphocytic diffusion is an early reaction to traumatic and other forms of synovitis. Discrete perivascular foci are the maximal reaction seen in chronic trauma and osteo-arthritis. Great numbers of lymphocytes are seen only in severe and chronic inflammations, e.g. tuberculous and rheumatoid arthritis, or together with neutrophils in subacute suppurative synovitis. Very large lymphoid foci and follicles seem to occur only in chronic progressive (rheumatoid) arthritis, where there is also synovial proliferation. Plasma cells may replace lymphocytes. Eosinophil infiltration is rare. Neutrophils predominate in pyogenic infections but are also present in rheumatoid and rheumatic fever arthritis.

Rheumatic fever synovitis is characterized by hyperaemia, oedema, fibrinous exudate, focal fibrinoid necrosis, neutrophil reaction, and little proliferation. The rheumatoid lesion has affinities with subacute or chronic bacterial arthritis but also shows features of its own. Histological diagnosis of rheumatoid arthritis is justified, but aetiological deductions are still speculative and can be made only by analogy. While comparisons are valid between different synovial lesions in man, caution is needed in comparing reactions in synovial and extra-articular tissues, and in applying to man the results of experiments on small animals.

Changes in the Skeletal Muscle of Patients with Rheumatic and Non-rheumatic Disease

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In 1945 Hugo Freund and Gabriel Steiner reported the presence of nodules of lymphocytes and plasma cells in the skeletal muscle of 100 per cent. of patients with rheumatoid arthritis and it was concluded that this lesion was specific for rheumatoid arthritis.

One purpose of our study was to determine the incidence of this cellular infiltrate in the skeletal muscle of: (a) normal persons, (b) patients with rheumatoid arthritis, (c) arthritis of types other than rheumatoid, and (d) patients with non-arthritic diseases. Another purpose was to determine whether the presence of cellular aggregates or muscle atrophy was associated with a significant change in the chemical composition of the muscle. Muscle was examined by biopsy from 202 persons, including 13 normal volunteers, 57 patients with rheumatoid arthritis, 10 with rheumatoid spondylitis (Marie-Strümpell), 21 with active rheumatic fever, 11 with inactive rheumatic heart disease, 19 with degenerative joint disease (osteo-arthritis), 10 with tuberculous arthritis, 8 with gout, and 53 with other diseases. Approximately 400 serial sections were made from each biopsy, and every fifth section was studied.

Lesions similar to those described by Freund and Steiner were found in 56 per cent. of patients with rheumatoid arthritis. Lesions indistinguishable from these, however, were found in three of the thirteen normal persons and in some patients with rheumatoid spondylitis, rheumatic fever, osteo-arthritis, tuberculous arthritis, gout, and subacute bacterial endocarditis, and also in several other diseases. These observations indicate that the muscle nodule described in rheumatoid arthritis is non-specific and probably of no diagnostic value.

Muscle samples obtained by biopsy from forty patients, including thirteen normal controls, were analysed for their contents of water, total protein, non-protein nitrogen, myosin, collagen, and adenosine-triphosphatase activity of the myosin. In patients with atrophy

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associated with various types of arthritis or with simple disuse, there were significant changes in muscle composition which included: (1) decrease in percentage of myosin and diminution of the adenosine-triphosphatase activity of the myosin; (2) fall in total protein content; and (3) absence of significant change in the average content of collagen. The changes in chemical composition correlated well with changes observed by histological study of sections simultaneously made from muscle samples analysed.

The Effect of Endocrines on Articular Tissues and their Relation to Ageing Processes

MARTIN SILBERBERG and RUTH SILBERBERG*

Growth processes and regressive changes occur spontaneously in the articular tissues of ageing mice. The changes manifest themselves in hyperplasia and hypertrophy as well as in destruction of the articular cartilage, outgrowth of bone, swelling of fibrinoid change of the interstitial substance of the ligaments, mucoid change or proliferation of the synovialis, and fibrosis of the bone marrow. These age changes differ in different strains of mice; they are genetically determined as to their onset, incidence, and severity, and are controlled by endocrine secretions. Moreover, the course of these age changes may be influenced by nutritional factors.

Administration of thyroid or sex hormones delays the time of appearance of the age changes in the articular tissues and decreases their incidence. Conversely, joint lesions can be produced in laboratory animals by the administration of anterior hypophyseal hormone or by removal of the sex glands. The changes thus produced are morphologically indistinguishable from those occurring spontaneously, although the former appear at an earlier age and are more frequent than the latter. The susceptibility to and the severity of these articular lesions may be decreased by caloric restriction and increased by feeding a high fat diet.

The findings in animals are comparable to those occurring in man as exemplified by material obtained from two cases of acromegaly and of four hundred human necropsies.

Osteo-arthritis is considered to be the result of the interaction of a tissue factor and a stimulus. The incidence, severity, and time of onset of degenerative joint disease depends on the relative intensity of these interacting principles. The tissue factor, manifesting itself in susceptibility to the disease, is controlled by such conditions as the genetic constitution of the individual, endocrine secretions, chronological age, and local blood and nerve supply. Stimuli may be of a mechanical, hormonal, or nutritional nature. The role of the endocrines in osteo-arthritis may then be two-fold: the endocrines may, by accelerating ageing processes, alter the susceptibility of the cartilage to injurious agents; or they may, in cases of endocrine disease, act as stimulating factors.

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Studies on the Possible Relationship of Pituitary-Adrenal Function to Arthritis

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In both normal subjects and in patients with rheumatoid arthritis, pituitary adrenocorticotrophic hormone stimulates the secretion of electrolyte-regulating, carbohydrate-regulating and androgenic adrenal steroids. A fall in the level of circulating eosinophils (direct determination) and an increase in the urinary excretion of uric acid represent sensitive indicators of the increased secretion of 11-oxy adrenal steroids. A marked increase occurs in the output of 17-ketosteroids in the urine; these are the excretory product of the increased production of androgenic adrenal steroids. Using the eosinophil change as a reflection of adrenal cortical function, we have investigated patients with rheumatoid arthritis, rheumatic fever, and gout by administering pituitary adrenocorticotrophic hormone. In selected subjects the initial eosinophil level provides a simple measure of adrenal cortical activity. Epinephrine was used to stimulate the pituitary-adrenal axis, and it produced a marked fall in circulating eosinophils and an increase in the excretion of 17-ketosteroids; but the anti-rheumatic effect was not produced, probably because of inadequate adrenal cortex stimulation.

The results of successful temporary treatment of patients with rheumatoid arthritis and rheumatic fever and gout by adrenocorticotrophic hormone confirmed the work of others. Data presented tended to show that patients with rheumatoid arthritis responded normally to epinephrine and adrenocorticotrophic hormone, and a provable adrenal insufficiency was not found. Of particular interest is the fact that the pituitary-adrenal system serves as a possible link between the effect of psychological and emotional factors on the measurable changes in vital metabolic processes.

The mechanism by which abnormally large amounts of adrenal cortical carbohydrate-regulating hormones alters the rheumatic process remains a subject for further work.

Chronic Polyarthritis and Psoriasis

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It appears from studies made at the Rheumatology and Dermatology departments of the Medical Clinics of the Medical Faculty of Barcelona, that the incidence of arthropathia psoriatica is very small, only about one-half of 1 per cent. of the patients seen in the rheumatological department presenting this disease. Almost uniformly the skin manifestations preceded the articular ones, in some cases by several years.

Though they seem to be more resistant to therapy, the skin lesions are no different, from the clinical and histological standpoint, from those seen in uncomplicated psoriasis. They occur most often in the scalp, trunk, elbows, and nails, in that order of frequency. The location

of the lesions in the distal interphalangeal joints, though more frequent than in other arthritides, is neither constant nor early. Vertebral localization is relatively frequent.

Periosteal reactions of the diaphysis, especially in the distal phalanges, are much more frequent than in rheumatoid arthritis; sometimes osteolytic mutilating lesions are seen in these locations. When the process is centred in the vertebral column, lesions similar to those seen in rheumatoid spondylitis are observed, with the exception that ligamentous calcification is exceptional.

We believe that the association of arthritis and psoriasis is rare and occasional.

Psoriasis and Arthritis : a Clinical Study of 115 Cases

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Over a period of approximately twenty years, 115 patients with psoriasis and arthritis have been observed in the arthritis clinics of the New York Hospital and the Hospital for Special Surgery, and in private practice. This constitutes the largest series of cases reported to date. Most cases were of typical rheumatoid arthritis. A certain number, however, differed from the classical picture in that the terminal phalangeal joints of the fingers and/or toes were involved, with and without involvement of other peripheral joints.

Resection Angulation Operation for Arthritis of the Hip

HENRY MILCH

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The treatment of arthritis of the hip presents one of the many still unsolved problems of medicine. Until the rheumatologist discovers a specific cure for the disease, the painful, deformed hip with limited or absent motion must continue to be treated surgically.

In the past many types of arthrodesis which seemed to offer relatively simple means of treatment of the painful hip have been devised. Increasing experience has, however, demonstrated that in over 30 per cent. of the successfully fused cases, whether young or old, intractable pain in the lumbar region is a sequel of the hip fusion.

More recently, a great variety of arthroplastic operations have been described for the release of already stiffened hips. Here, too, experience has unfortunately demonstrated the relative inadequacy of this approach to the problem.

To avoid the reproaches inherent in both these types of procedure, a method has been devised which is based on the concept that the criteria of successful therapy are kinesiological and not anatomical. In principle, the operation is a combination of two earlier, well tried procedures: (1) excision of the femoral head and neck to restore mobility, and (2) angulation osteotomy in the coronal plane (Schanz type) to re-establish stability.

Through a lateral ilio-femoral incision (Watson-Jones) the capsule of the hip is exposed and opened. The femoral neck is transected at its base and the head and neck are removed en masse. Following this, the lateral aspect of the femur is subperiosteally exposed and a subtrochanteric osteotomy is performed. The lower fragment is abducted until the angle it makes with the upper fragment is congruent with the inclination of the wall of the levelled pelvis on the same side. The fragments are fixed by means of an angulated nail so that early motion can be instituted. A simple internal rotation splint is used to prevent external rotation of the thigh.

The operative intervention is exceedingly simple. It is accompanied by relatively little shock and may, therefore, be indicated in older patients. No plaster immobilization is used and the patient may consequently be allowed out of bed, walking with the aid of crutches within three to six weeks after operation. No stiffness of the knee and ankle has been observed.

Originally performed in two stages, the earlier operation has been completely revised, and since 1946 has been completed at a single sitting. It has been employed in about twenty cases of hip joint disability following upper femoral epiphyseolysis, tuberculosis, Marie-Strümpell's disease, old pyogenic infection, old congenital dislocations, and fractures of the femoral neck with avascular necrosis or arthritis, in advanced osteoarthritis; and in two cases in which previous arthroplasties had been unsuccessful. In all cases it was possible to restore stability and mobility, provided the motor power of the hip muscles was adequate. In several cases some pain has persisted. In one case this was overcome by the resection of the obturator nerve, in two others by removal of the projecting screws. On the whole the patients have been satisfied and the results have been sufficiently encouraging to warrant wider use of the method.

Pathological Anatomy of Collagen Diseases

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At present the term " collagen disease " refers to a group of clinically heterogeneous, symptomatically puzzling diseases, such as systemic lupus erythematosus, generalized scleroderma, and probably dermatomyositis. They are characterized anatomically by systemic alterations of the connective tissue, in particular by an abnormality of its extracellular portions. This abnormality expresses itself microscopically as fibrinoid alteration and sclerosis of the collagen fibres and an increase of the metachromatic ground substance.

Such connective tissue changes alone, however, are not pathognomonic. They are observed in maladies of clearer definition, such as rheumatic fever, rheumatoid arthritis, and periarteritis nodosa. They also occur locally and can be provoked experimentally. It must, therefore, be the object of morphologic investigations to search for additional structural criteria and to evaluate their reciprocal relationship in the different diseases which involve the connective tissue. For instance the

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recent observation of depolymerization of desoxyribose nucleic acid of mesenchymal cells in systemic lupus erythematosus introduces a new characteristic for the morphologic definition of this malady. Furthermore, it is the aim of anatomical pathology to advance beyond mere description and to inquire into the mechanism responsible for generalized connective-tissue alterations.

The Protean Nature of the Connective Tissue Diseases

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In recent years there has been an increasing tendency to speak collectively of rheumatoid arthritis, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis, and generalized scleroderma as " connective-tissue diseases ". The demonstration of widespread morphological alterations in the fibrous connective tissues has led to the concept that these diseases, protean in nature, may be related. This is in sharp contrast to the traditional concept that they are clinically distinct and unrelated.

Deserving of emphasis is the fact that all these diseases have many manifestations in common. All are systemic diseases with varied constitutional, vasomotor, gastrointestinal, and articular symptoms. All may show mucocutaneous, haemorrhagic, cardiac, and neuromuscular lesions, and in all there may be generalized lymphadenopathy, serositis, alterations in leucocyte counts, and subcutaneous nodules.

Certain prominent or characteristic features are of diagnostic value. Rheumatoid arthritis is characterized by progressive, symmetrical arthritis. Ocular involvement, most often uveitis, or the presence of subcutaneous nodules may antedate the arthritis and serve as the clue to the final diagnosis. Renal disease is rare as a manifestation of this disease. In rheumatic fever cardiac involvement is the most significant manifestation. The arthritis is migratory in nature and rarely causes persistent inflammation of peri-articular structures. The presence of chorea or of erythema marginatum is presumptive evidence of rheumatic fever. A leucopenia is very unusual. The clinical picture of lupus erythematosus disseminatus is variable. The presence of a typical skin rash, serositis, arthritis, leucopenia, and renal disease in a patient with fever and other constitutional symptoms makes the diagnosis probable. The articular involvement may be indistinguishable from that seen in rheumatoid arthritis and rheumatic fever. In contradistinction to rheumatoid arthritis, spinal involvement and advanced destruction of articular cartilage are uncommon. Skin and renal involvement may be long delayed; in the absence of both, the diagnosis is probably not warranted. Periarteritis nodosa is suggested by various combinations of the following features: renal disease, hypertension, peripheral neuritis, abdominal pain, muscle pain and tenderness, asthma, leucocytosis, and eosinophilia of impressive degree. Rarely are these features all present. Dermatomyositis, once well established, is characterized by emaciation, induration of subcutaneous tissues, marked weakness, atrophy and contractures of skeletal muscles, and frequently calcinosis. Early in the disease the clinical picture may simulate closely that of rheumatoid arthritis or lupus erythematosus disseminatus. The characteristic feature of scleroderma is the tight, waxy, adherent skin with areas of pigmentation and depigmentation. Pulmonary fibrosis, cardiac dilatation, disturbances of gastrointestinal motility, and vasomotor symptoms are other prominent manifestations.

In isolated cases, however, the clinical features considered characteristic of one or another of these diseases may overlap to such an extent that diagnosis is difficult and at times impossible. Rarely, the pathological features characteristic of two or more different diseases occur coincidentally. Thus, a patient with lupus erythematosus disseminatus showed at autopsy a necrotizing panarteritis similar to, if not identical with, periarteritis nodosa; a patient with dermatomyositis showed the lesions of both dermatomyositis and scleroderma, as well as a proliferative endarteritis and segmental necrotizing arteritis. On the other hand Aschoff bodies, lesions considered to be pathognomonic of rheumatic fever, have been seen in one typical case of periarteritis nodosa. Thus the clinician may ask the pathologist: How often is the distinction between these diseases made on a quantitative rather than a qualitative basis ?

Despite the fact that these diseases usually conform to dissimilar disease patterns and differ in prognosis, the many overlapping features are noticeable. The existence of cases with pathological lesions characteristic of two or more of these diseases also suggests a relationship among them. The exact nature of this relationship with regard to aetiology and pathogenesis is unknown. It is emphasized that rigid adherence to arbitrary diagnostic criteria may obscure clues pointing to common pathogenic mechanisms. Such clues are of importance in orienting the investigative approach to these diseases.

Therapeutic Criteria and Related Aids in Rheumatoid Arthritis

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This report summarizes recommendations for uniform therapeutic criteria in rheumatoid arthritis. A definition of rheumatoid arthritis is included, which closely follows that established by the American Rheumatism Association; this is to prevent the inclusion of doubtful cases in reporting results.

The primary considerations in undertaking the treatment of a patient with rheumatoid arthritis are: (1) to diagnose accurately; (2) to determine the stage of the disease (Table 1) ; (3) to determine the degree of functional capacity (Table 2).

For the purpose of evaluating the response of rheumatoid activity to any treatment, the signs of active disease presented by the patient at the initial examination

TABLE 1
CLASSIFICATION OF RHEUMATOID PROGRESSION

Stage	Radiographic signs	Muscle atrophy	Extra-articular lesions (nodules: teno-vaginitis)	Joint deformity	Ankylosis
I	Osteoporosis, sometimes no destructive changes	0	0	0	0
II	Osteoporosis, slight cartilage or subchondral bone destruction may be present	Adjacent	May be present	0	0
III	Osteoporosis, cartilage destruction, bone destruction	Extensive	May be present	Subluxation, ulnar deviation and/or hyperextension	0
IV	Same as III with bony ankylosis	Extensive	May be present	Same as III	Fibrous or bony ankylosis

TABLE 2
CLASSIFICATION OF FUNCTIONAL CAPACITY

I	Complete: Ability to carry on all usual duties without handicaps.
II	Adequate for normal activities: Despite handicap of discomfort or limited motion at one or more joints.
III	Limited: Only to little or none of duties of usual occupation or self care.
IV	Incapacitated, largely or wholly: Bedridden or confined to wheel chair; little or no self care.

constitute the maximum evidence of rheumatoid activity in that individual, and form the basis for determining response to therapy by decrease in those signs of activity. Such responses to therapy may be divided into four grades: I, complete remission; II, major improvement; III, minor improvement; IV, no improvement or progression (Table 3). Whenever possible precision instruments, such as tape measure and goniometer, should be used in estimating the degree of swelling and motion, for the purpose of reporting the progress of the disease under therapy.

It is urged that an arbitrary time limit be established for initial therapeutic response for each method of therapy. This is because the disease has natural fluctuation, remissions, and exacerbations. This arbitrary time limit should be long enough to exclude the

TABLE 3
RESPONSE OF RHEUMATOID ACTIVITY TO THERAPY

GRADE	Systemic signs	Signs of joint inflammation	Signs of extra-articular activity	Remaining impairment of joint mobility	Articular deformity	Erythrocyte sedimentation rate	Radiographic signs
I Complete remission	0*	0*	0*	Due only to irreversible changes	Due only to irreversible changes	0*	No progression
II Major improvement	Elevated erythrocyte sedimentation rate and/or vasomotor imbalance permissible	Only minimum* residual joint swelling (no new sites)	Minimum* (no new sites)	Only consistent with minimum residual activity	Due only to irreversible changes	May be elevated	No progression
III Minor improvement	Decreased*	Only partially* resolved (no new sites)	Decreased* (no new sites)	In relation to residual inflammation	May be present	May be elevated	No progression
IV Unimprovement	Undiminished*	Same* or worse	Same or new sites or exacerbation*	Same, better or worse	Present or not	Any rate	Changes indicative of progression

* Indicates criteria required to be present.

factor of spontaneous remission. Furthermore, to avoid errors arising from misinterpretation of the natural fluctuations of the disease, it is recommended that "minor improvement" (Grade III) should not be considered significant and should not be included in any statistical survey of a therapeutic agent or procedure. This is to avoid misleading lumping of "favourable" results.

Classification of "functional impairment" together with the "criteria for therapeutic response" can give a helpful insight into the usefulness of the whole treatment programme, which may include such general procedures as physical therapy, psychotherapy, orthopaedic measures, etc., but for the purpose of evaluating a specific therapeutic agent, it is recommended that reports of such treatment should be based only on the "criteria for therapeutic response in rheumatoid activity".

Heredity in Rheumatoid Arthritis and Ankylosing Spondylitis

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The heredity and family incidence of rheumatoid arthritis, spondylitis, and rheumatic fever was studied by comparing the family histories of patients with rheumatoid arthritis and of those with spondylitis with each other and with the families of several control series. The latter consisted of 77 families of patients with Heberden's nodes, 38 families of patients with gout, and 84 other families of patients with none of these diseases. Rheumatoid arthritis occurred in the fathers, mothers, and sisters of rheumatoid patients in a significantly higher proportion than it did in the relatives of patients with spondylitis or in the controls.

Spondylitis occurred in the brothers and sisters of spondylitis patients and of rheumatoid arthritis patients more than it did in any other group. Rheumatic fever occurred much more frequently in the patients with rheumatoid arthritis and with spondylitis than in any other groups.

Adrenocortical Dysfunction in Gout

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Evidence reported suggests that androgen activity in gouty patients may be maintained by an abnormal male sex hormone which contributes only slightly to urinary 17-ketosteroid excretion. This hormone does not seem to be present in patients with non-gouty hyperuricaemia or in rheumatoid arthritis. The "gouty androgen" appears to originate in the adrenal cortex and to be secreted under conditions similar to those which control secretion of normal androgen. Gouty androgen appears to be opposed by oestrogens. Normal sex difference in plasma urate concentration may be controlled by normal androgen and gouty hyperuricaemia may be controlled by "gouty androgen".

Acute hypofunction of the adrenal cortex with respect to production of 11-oxysteroids may provide the necessary setting for an attack of gouty arthritis. This deficiency may result from endogenous metabolic changes, from increased demand for 11-oxysteroid due to stress, or withdrawal of adrenocorticotrophin.

Increased production of 11-oxysteroid compounds may terminate an attack of gouty arthritis.

Production of an abnormal androgen by the adrenal cortex and deficient response of the cortex to demands for 11-oxysteroid are characteristic features of adrenal cortical function in gouty patients.

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Pleuropneumonia-like Organisms and their Possible Relation to Articular Disease

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Organisms of the pleuropneumonia group are often recovered from the mucous membranes of humans. In animals similar organisms produce highly infectious diseases. The tendency of these organisms to localize in joints in animals producing a fleeting migratory arthritis and also ankylosing chronic arthritis is of interest in relation to the study of rheumatic diseases in humans. The pleuropneumonia group of organisms is characterized by being much smaller in size than most bacteria and by a peculiar reproductive process in which the smallest elements of the colonies become swollen into large round forms from which the small elements subsequently grow out and again repeat the cycle. This process contrasts sharply with the usual method of multiplication in bacteria namely, binary fission. The organisms are ordinarily not visible in tissues, and the diseases caused by them were in most instances regarded as virus diseases. Culture and identification are often difficult, requiring special methods. Transfer to experimental animals is usually not applicable, because pleuropneumonia organisms are specialized to one host.

It is significant that certain common bacteria, including typhoid, paratyphoid, dysentery, *Proteus*, *Streptobacillus moniliformis*, *H. influenzae*, and saprophytic Gram-positive organisms, may under appropriate conditions undergo transformation into forms indistinguishable from organisms of the pleuropneumonia group. Penicillin produces this transformation in many species of bacteria. A similar transformation has been observed in typhoid bacilli upon exposure to antibody and complement.

Although pleuropneumonia-like organisms may be recovered from the normal genital tract, they are more frequently found in association with inflammatory processes. In males, the genito-urinary infections may extend into the prostate and bladder and may be

associated with acute articular involvement. However, the aetiological significance of pleuropneumonia-like organisms is as yet not fully understood. The unusual transformation of bacteria into a form not recognizable by the usual bacteriological methods and having different susceptibility to antibiotics raises new problems in the study of infectious diseases and may be of special interest in rheumatic diseases.

Antigenic Properties of Hyaluronidase Introduced into the Study of Rheumatic Diseases

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Intradermal injections of 1:1,000 hyaluronidase (0·15 TRU per ml.) with 1 per cent. methylene blue were given to 81 individuals to determine the incidence of skin sensitivity in arthritics and controls. The results were positive in 59 of 62 patients with atrophic arthritis, in 1 of 3 patients with hypertrophic arthritis, and in 7 out of 8 patients with mixed types. Only one of the controls showed a slightly positive test.

In a number of the patients exhibiting positive tests, a cutaneous nodule developed which lasted from three to fourteen days. Round cell infiltration, thickened and collagen fibres, small areas of necrosis, and occasional eosinophils and giant cells were seen in the several instances in which a biopsy was performed.

Twelve patients with atrophic arthritis were given a series of injections of small amounts of hyaluronidase in an attempt at desensitization. In seven of these, improvement was manifested by decrease in pain, increase in chest expansion and range of motion in the extremities, and increased strength.

Antibodies can be demonstrated in the serum. Before treatment the average titre is 1:32. Following the series of desensitizing injections, the titre may rise to 1:32,768. The skin test occasionally becomes negative after treatment.

It is concluded that sensitivity to hyaluronidase may play a part in the development of arthritic changes, in view of the tissue response at the site of injection. It is also considered possible that desensitization may alter the course of the disease.

Familial Aspects of Gout

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Three series of gouty patients and non-affected relatives have been studied in recent years. These researches have been pursued in Ann Arbor, Cleveland, and Boston. The fourth series is now being investigated in Buffalo. The results are similar and the tentative conclusions significant. Approximately 25 per cent. of non-affected relatives of gouty patients have a hyperuricaemia when sampled at random ages. Presumably this percentage decreases in each decade of life since an occasional non-affected relative with hyperuricaemia will develop gouty arthritis and will no longer be classified as a non-affected relative. The age at which hyperuricaemia appears has not been determined; possibly it is associated with puberty. The statistical evidence suggests that hyperuricaemia in gouty families is a single autosomal dominant gene. The mechanism whereby the dominant manifests itself is still uncertain. The strength of the dominant, that is, the degree of elevation of serum uric acid, the duration of the metabolic dyscrasia, or an as yet unrecognized factor, may all participate.

An enlightened approach to the care of gouty families would be the periodic examination of the serum of all relatives of gouty patients. These familial studies lend support to the hypothesis that the pathogenesis of gouty arthritis is related to an increased formation of uric acid by the body rather than to impaired excretion.

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Role of the Anterior Pituitary and Adrenal Cortex in Urate Metabolism and in Gout

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These endocrine factors have been studied by observing (1) the effect of adrenocorticotrophic hormone on urate metabolism in normal and gouty patients and on the course of acute gout, (2) 17-ketosteroid excretion in gouty patients, (3) the effects on metabolism and clinical gout produced by stimulating the anterior pituitary with epinephrine, and (4) the effect of colchicine on the pituitary-adrenocortical mechanism. In addition to blood and urine urate determination by a specific enzymatic method, other indices of pituitary-adrenocortical activity included nitrogen balance, carbohydrate tolerance, electrolyte and water excretion, 17-ketosteroid excretion, and changes in haematology.

Adrenocorticotrophic hormone produces a marked increase in urate excretion in normal individuals without a significant fall in blood urate. The chief differences in a gouty patient given the hormone during an asymptomatic period were a sharp decrease in true blood urate to less than 50 per cent. of the base line levels, and the absence of any evidence of rebound in pituitary-adrenocortical activity in the post-injection period; acute gout developed on the third post-injection day. Acute gout following tophectomy was not associated with any evident change in adrenocortical function. Injection of the hormone resulted in prompt temporary amelioration of symptoms on two occasions, and was followed by indications of adrenocortical stimulation.

Epinephrine in doses of 1·5 mg. intravenously had no effect on acute gout. When given to an asymptomatic gout patient intravenously, or intramuscularly in divided doses of 6 mg. daily, no metabolic effects were noted except a decrease in eosinophils. Twenty-six determinations of 17-ketosteroid excretion in ten patients with gout gave values consistently lower than normal, both during attacks and in interval periods. Colchicine, in doses of 4 to 5 mg. orally and 2·0 mg. intravenously, produced no change in eosinophil counts or nitrogen

balance in patients with gout. Effects on blood and urine urate levels were inconstant.

Tentative conclusions to date are: (1) the adrenal cortex has a profound influence on urate metabolism, (2) its effect in gouty patients differs in some respects from that in normal subjects, (3) gout is characterized by a low excretion of 17-ketosteroids, (4) the adrenal cortex of gouty patients can respond to stimulation, both during interval periods and at times of acute attacks. There is suggestive but not conclusive evidence that acute attacks tend to occur at times of decreased adrenocortical activity, and that the latter is the result of sluggish production or activation of endogenous adrenocorticotrophic hormone under the same conditions in which normal persons demonstrate evidence of a sharp increase in activity of endogenous adrenocorticotrophic hormone. Epinephrine appears to be an unsatisfactory method of stimulating pituitary-adrenocortical activity in gouty patients. The mode of action of colchicine through an endocrine mechanism has not been established.

Fundamental Investigations on the Synovialis: an Approach to the Nature of Arthritis

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A study was undertaken with new techniques of the fundamental physiology of the synovialis. Some earlier efforts had been confined to single static determinations *in vitro* or *in vivo* by means of an electrode inserted into the synovial cavity with a reference electrode inserted subcutaneously. These experiments were done continuously to allow the reaction to be followed over a long period. Another electrode inserted in the femoral vein made possible simultaneous continuous study of the changes in the blood from the general region of the joint studied. This study was of value in the evolution of procedures involving many factors integrated in varying proportions under different conditions (*Amer. J. Physiol.*, 1946, **146**, 1.)

The next step was to study the influence of vasomotor control by means of perivascular sympathectomy which produced, generally, permanent vasodilation. After stimulation of the femoral nerve the *p*H in the vein fell transiently on the normal side, and markedly over a long period on the sympathectomized side. Massage of a normal knee joint facilitated recovery from stimulation of the nerve. On the sympathectomized side it tended to lower *p*H still further, because acidic fluid was forced from the tissues into the synovial cavity. Convulsions produced by insulin or metrazol gave rise to effects comparable to those resulting from nerve stimulation.

By this time it had become apparent that the synovial membrane is an actively metabolizing tissue. Consequently, it appeared feasible to study membrane potentials and the influences of various ions thereon (*Amer. J. Physiol.*, 1948, **153**, 364). This led directly to a study of enzyme systems. When known enzyme inhibitors or activators were injected while the potential was being determined, it was possible to get a quantitative picture of the metabolic reactions occurring. In general positive millivoltage indicates a quiescent state or at least a less active state, while negative potential indicates greater activity.

Further studies are under way to determine how these facts may be integrated and modified in relation to pathological changes in the joints preliminary to arthritis.

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Factors Associated with the Onset of Rheumatoid Arthritis: A Statistical Study of 293 Patients and Controls

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Results are presented from a statistical study of 293 unselected patients with rheumatoid arthritis and a similar number of controls of corresponding age and sex. Of the patients studied, 64 per cent. were women, but this ratio was reversed in the thirty-nine patients with spinal involvement. Special localizations of other diseases show a similar change in sex ratio. The findings for the age of onset were compared with the census figures for the age distribution of the population of Massachusetts and the χ^2 test was applied. No significant departure was found in men, but in women a marked increase was discovered in the age group 50 to 54. An influence of the menopause is thus suggested, but these studies show no close relationship between the cessation of menstruation and the onset of the disease.

A significantly increased familial incidence of both rheumatoid arthritis and rheumatic fever was found in patients as compared with controls, but the evidence is not sufficient to establish an hereditary factor. No relationship could be shown between rheumatoid arthritis and disease of known allergic origin on the basis of familial or personal incidence of allergic manifestations. A symmetrical distribution of joint involvement was present from the onset in 70 per cent. of the 262 patients whose disease began in peripheral joints. Contrary to opinion expressed in the literature, large and small joints were primarily affected with equal frequency and those of the legs more often than those of the arms. The onset was monarticular in one-sixth of the patients, all of whom eventually suffered from polyarthritis. In one-half of the patients who had spondylitis on admission the arthritis first appeared in peripheral joints, almost invariably of the lower extremities.

The onset of definite arthritis was usually preceded by constitutional symptoms or precipitating factors or both. In the former group it was established by questioning both patients and controls that fatigue and anorexia were prodromal symptoms. Strain, either mental or physical, and acute infections most commonly preceded the onset of arthritis, with exposure to cold or dampness, surgical operations, trauma, and, infrequently, childbirth. The data suggest that prodromal constitutional symptoms may mark the real onset, and that

so-called precipitating factors merely arise in a more easily recognizable phase, with articular localization of the morbid process.

Gold Toxicology and Rheumatoid Arthritis with Particular Emphasis on Bone Marrow Studies

CHARLES LEROY STEINBERG
Rochester, New York

One hundred and seven typical cases of rheumatoid arthritis were treated with gold thioglucose in oil. The initial dose was 40 mg., which was followed the week after by 60 mg., and then in most instances 100 mg. were given weekly intramuscularly.

A total of 154 bone marrow aspirations were done on 90 of the cases. Thirty-two patients developed skin manifestations. Four developed varying degrees of thrombocytopoenia. One developed maturation arrest of the granulocytes in the bone marrow. Ten instances of albuminuria with erythrocytes as a cause of albuminuria were noted. Two patients developed untoward gastro-intestinal symptoms, and had hyperpyrexia. Thus, fifty instances of gold toxicity were noted.

Eosinophilia of the bone marrow preceded the skin manifestations by several weeks. When the peripheral platelet count dropped, a bone marrow aspiration was done. Gold treatment could be continued in those cases in which the bone marrow was normal, but had to be stopped if megakaryocytes and platelets were scarce.

Severe instances of gold dermatitis responded well to BAL treatment. Gold treatment was not contra-indicated in those patients developing mild to moderate skin manifestations at a later date. Gold should be discontinued in patients developing suppression of the bone marrow elements. Gold treatment was not renewed in those patients who developed marked albuminuria.

Biopsy of the bone marrow should be done as a routine in patients receiving gold treatment.

RÉSUMÉ

Le Septième Congrès International des Maladies Rhumatismales s'est tenu à New York du 30 mai au 3 juin 1949. On trouvera ci-dessus les résumés des plus importants articles lus au Congrès. Malheureusement, le manque de place ne nous permet pas de publier leur traduction française, mais pour référence nous indiquons ici leurs titres français.

Titres	*Auteurs*
Histopathologie des tissus conjonctifs.	S. H. Bensley et A. W. Ham.
Distinction pathologique entre l'ostéo-arthrite et l'ostéophytose vertébrale.	D. H. Collins.
Diagnostic de l'ostéo-arthrite.	A. M. Davison.
Histopathologie du système neuro-musculaire dans l'arthrite rhumatismale.	L. R. Morrison et coll.
Génèse périphérique de la douleur.	J. H. Kellgren.
Maladies dues au surmenage et à l'usure du muscle strié.	H. Seyfarth and K. Møinichen.
Effet du Δ-5-pregnalone sur l'excretion urinaire des 17-cétostéroïdes et la symptomatologie de la spondylite ankylosante.	R. A. Davison et P. Koetz.
Oestrogènes synthétiques dans le traitement de la spondylite ankylosante.	F. Coste et S. Bonfils.
Membrane synoviale dans l'ostéo-arthrite.	R. E. Ghormley et J. R. Bateman.
Etendue des réactions pathologiques pouvant se produire dans les tissus synoviaux humains.	D. H. Collins.
Altérations histologiques et chimiques dans les muscles des malades rhumatiques et non-rhumatiques.	J. J. Bunim et coll.
Valeur thérapeutique des sels du cuivre dans l'arthrite rhumatismale.	J. Forestier et coll.
Effet des sécrétions endocrines sur les tissus articulaires et leur rapport aux processus de vieillir.	M. and R. Silberberg.
Etudes sur le probable rapport entre la fonction adréno-pituitaire et l'arthrite.	G. W. Thorn et coll.
Polyarthrite chronique et le psoriasis.	P. Barcelo et coll.
Opération de résection-angulation dans l'arthrite de la hanche.	H. Milch.
Anatomie pathologique des malades collagènes.	P. Klemperer.
Nature protéique des maladies du tissu conjonctif.	W. Bauer et coll.
Critères thérapeutiques et aides associées dans l'arthrite rhumatismale.	C. H. Traeger.
Hérédité dans l'arthrite rhumatismale et dans la spondylite ankylosante.	R. M. Stecher et coll.
Troubles de la fonction adréno-corticale dans la goutte.	W. Q. Wolfson et coll.
Micro-organismes similaires à ceux de la pleuro-pneumonie et leur possible rapport avec la maladie articulaire.	L. Dienes.
Propriétés antigéniques de la hyaluronidase appliquées à l'étude des maladies rhumatismales.	C. E. Logan.
Aspect familial de la goutte.	J. H. Talbot.
Rôle de l'hypophyse antérieur et de la cortico-surrénale dans le métabolisme des urates et dans la goutte.	W. D. Robinson et coll.
Investigation fondamentale de la synoviale ; une approche à la nature de l'arthrite.	C. E. Reed et coll.
Facteurs associés au début de d'arthrite rhumatismale : étude statistique de 293 malades et témoins.	C. A. Short et coll.
Toxicologie de l'or et l'arthrite rhumatismale, avec accent particulier sur l'étude de la moelle osseuse.	C. L. Steinberg.

ABSTRACTS

[This section of the ANNALS *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; general pathological articles; other general articles. At the end is a list of articles that have been noted but not abstracted. Not all sections may be represented in any one issue.]*

Acute Rheumatism

Rheumatic Pneumonitis in Childhood. LEVY, H. B., COFFEY, J. D., and ANDERSON, C. E. (1948). *Pediatrics*, **2**, 688.

The authors report 6 cases of rheumatic pneumonitis with post-mortem findings in 5. They describe the Masson body or granuloma, focal fibrinoid necrosis and alveolitis, arteriolitis, and septal-cell proliferation. No therapeutic measures seemed to be of value. They emphasize that rheumatic pneumonitis is of grave prognostic significance. *R. S. Illingworth.*

Immunologic and Biochemical Studies in Infants and Children, with Special Reference to Rheumatic Fever. IV. Occurrence of Agglutinins in Normal and Abnormal Conditions. DEGARA, P. F. (1948). *Pediatrics*, **2**, 410.

In order to test the hypothesis that an adequate immune response may be an important factor in rheumatic fever, the author studied the degree of production of agglutinins for *Streptococcus haemolyticus* in both normal and rheumatic individuals. They obtained no evidence to indicate that the immune response of "susceptible" and rheumatic children to infections, presumably streptococcal in origin, is different from that of non-rheumatic subjects. *P. T. Bray.*

Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever. V. Electrophoretic Patterns in Blood Plasma and Serum in Normal Children. LUBSCHEZ, R. (1948). *Pediatrics*, **2**, 570.

This is a study of the electrophoretic patterns of the blood of 57 normal healthy children ranging in age from under 1 to 11 years. The children were divided into two groups, one of 30 who had had no illness within 4 months of the study, and the other of 27 who had had various illnesses in that period. In the first group, the mean values for the relative concentrations of the various plasma proteins were in close agreement with those obtained by Dole (*J. clin. Invest.* 1944, **23**, 708) in normal adults, except that the greatest variation from the mean, which occurred in the albumin and gamma globulin fractions, was several times larger than that obtained by Dole. In the second group, the value for beta globulin remained unchanged, whereas the other components differed from the first group by about one standard deviation, the albumin level being decreased and the remaining globulin levels increased. Abnormal values occurred in all components except beta globulin, 44% having gamma globulin levels over 16·7%. The frequency of the abnormalities was related directly to the duration and severity of the illness, and to the interval between the illness and the investigation.

Marianna Clark.

Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever. VI. Electrophoretic Patterns of Blood Plasma and Serum in Rheumatic Children. WILSON, M. G., and LUBSCHEZ, R. (1948). *Pediatrics*, **2**, 577.

The electrophoretic patterns of the blood of 42 rheumatic children were analysed. It is concluded that the immunological response of rheumatic children to streptococcal infection does not differ from that of non-rheumatic subjects, and that any elevation of the γ globulin component in rheumatic fever is a function of an antecedant streptococcal infection and not of the rheumatic process.

Salicylate Medication in the Treatment of Acute Rheumatism in Childhood. Study of Salicylate Levels in the Blood. (La medicación salicilada en el tratamiento de la enfermedad reumática del niño. Estudio de los neveles salicilémicos.) CORREA, B. D. (1948). *Arch. brasil. Cardiol.*, **1**, 285.

Serum salicylate levels were estimated in 56 cases of rheumatic fever in children. Given by mouth the concentration of the drug in the blood reached its maximum in 1½ to 2 hours, and fell to a low level within 4 hours; the addition of sodium bicarbonate tended to lower the serum salicylate level. Given intravenously, the drug reached a high concentration within 20 minutes, the level falling slowly in the following 4 hours. Rectal administration of salicylate resulted in a moderate serum concentration in 30 minutes, gradually rising to a maximum in 3 hours. With a daily dose of salicylate from 0·1 to 0·2 g. per kg. body weight serum values of 150 to 250 mg. per 100 ml. were obtained. This concentration of salicylate was clinically effective, but above 325 mg. per 100 ml. toxic manifestations appeared.

The author discusses various theories of the mode of action of the salicylates. *Paul B. Woolley.*

Psychological and Social Aspects of Sydenham's Chorea. WALKER, E. R. C. (1949). *Edinb. med. J.*, **55**, 17.

The author describes detailed psychological investigation of 42 patients with Sydenham's chorea. Eighty per cent. of the children were from urban districts, and there was a greater incidence of the disease in crowded areas. War conditions were associated with diminished liability to chorea.

Special analysis of the series revealed the following facts: (1) 11 of the choreic children were from families of 2. (2) The disease had a predilection for the youngest in a family. (3) In 34 cases the mother showed undue excitability, irritability, anxiety, or other temperamental quality likely to engender in the child a feeling of apprehension or uncertainty. The impression was that the mothers of choreic children tend to be anxious-minded women living under strain, usually over-conscientious.

and often with strong scholastic or social ambitions for their children. (4) Paternal influence appeared less important. (5) In over two-thirds of the cases there was a disturbing factor in the relationship of the child with one or more of the brothers and sisters. (6) Adverse home conditions and housing conditions, especially overcrowding, were found in nearly all cases. (7) Economic factors were less important, though closely related to the last. (8) The "school factor" was less frequently present than had been expected.

In no single case could it be said that the child was being brought up in a comfortable, decent home by stable parents unhampered by gross financial difficulties, and was leading a normal happy school life.

The author rejects the traditional concept that the proven association of chorea and juvenile rheumatism implies a causal relation, and postulates that chorea is an affective disturbance induced by subjection to psychological stresses from which the child can find no satisfactory escape. If this disturbance is sufficiently severe or long-continued it produces the hyperkinesis and hypotonia very probably through cortico-thalamic exhaustion. The nature of the association between chorea and juvenile rheumatism he explains by stating that their causes commonly but not necessarily occur in conjunction as concomitants of poverty and overcrowding. *P. T. Bray.*

The Squeezogram : An Objective Method for Recording the Course of Chorea. COHEN, J. J., and DANCIS, J. (1948). *J. Pediat.*, **33**, 564.

A graphic method for recording the severity of choreiform movements is described. The original should be consulted.

A Preliminary Report on Rheumatic Fever in Virginia. MCCUE, C. M., and GALVIN, L. F. (1948). *J. Pediat.*, **33**, 467.

The authors present a statistical analysis of 225 cases of rheumatic fever which had been followed for at least three years or until death. The average duration of the disease was 5·95 years. There was a positive family history in 17·3%, and a history of preceding haemolytic streptococcal infection in 50%. The mean duration of the first attack was 6·4 months, and of the second attack 8 months. Cardiac involvement occurred in 83% during the active phase. Residual cardiac damage was found in 49%, but the period of observation was short. During the period 7·1% of the patients died. *R. S. Illingworth.*

Orally Administered Penicillin in Patients with Rheumatic Fever. MASSELL, B. F., DOW, J. W., and JONES, T. D. (1948). *J. Amer. med. Ass.*, **138**, 1030.

Penicillin was given in the form of buffered tablets one hour before meals in doses of 300,000 to 1 million units per day, for 10 days, to patients with rheumatic fever in whose throat haemolytic streptococci had been found. The organisms were eradicated from the throat in 28 of 37 cases. Failure to eradicate the organisms in the remaining cases could not be ascribed to the development of penicillin-resistance or to other known factors. The organisms were suppressed during the period of treatment in all but 2·1% of the cases. The prompt treatment of active streptococcal infection and the reduction in the streptococcal carrier rate did not prevent the spread of streptococcal infection among ward patients. In 10 clinical and 5 subclinical infections with group A haemolytic streptococci treated promptly with oral or intramuscular penicillin, no recurrence of rheumatic fever occurred. Though it was realized that other factors might explain this, it was felt that this freedom from relapse was worthy of further investigation. The possible value of prophylactic oral penicillin in the prevention of rheumatic fever by this suppresson of haemolytic streptococcal infections is discussed. *R. S. Illingworth.*

Longevity in Rheumatic Fever. Based on the Experience of 1,042 Children Observed over a Period of Thirty Years. WILSON, M. G., and LUBSCHEZ, R. (1948). *J. Amer. med. Ass.*, **138**, 794.

From the records of 1,042 children observed over a period of up to 30 years an attempt is made to assess the expectation of life in children with rheumatic fever. Longevity in relation to age and duration of the disease is discussed. The mean age of onset is 6·5 years, and the chief danger periods are the first year of the disease and puberty, irrespective of the age of onset. The low morbidity and mortality rates in those surviving puberty are emphasized. Death was due to rheumatic heart disease in 75% of cases and to subacute bacterial endocarditis in 10·2%. *K. M. Lawther.*

Intracranial Vascular Lesions in Late Rheumatic Heart Disease. DENST, J., and NEUBUERGER, K. T. (1948). *Arch. Path.*, **46**, 191.

The authors describe intracranial vascular lesions seen in the late stages of rheumatic heart disease. Of the 14 cases in which adequate examination of the brain was made, significant changes were found in 9. Vessels affected were the small, medium-sized, and larger basal arteries, and the veins of the leptomeninges. The chief lesions were varying forms of thromboses, endarteritic proliferation, thickening and splitting of the internal elastic lamina, and fibrosis of the media and adventitia. *R. H. Heptinstall.*

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Juvenile Rheumatoid Arthritis. LOCKIE, L. M., and NORCROSS, B. M. (1948). *Pediatrics*, **2**, 694.

The authors describe the course of 28 cases of rheumatoid arthritis which began before the age of 12. In the 2 youngest the disease started at the age of 12 months. The ratio of females to males was 2·5 to 1. In 10 cases there was a history of preceding respiratory infection, and in 3 a history of preceding trauma.

In discussing treatment they emphasize the importance of complete rest in bed, with suitable physiotherapy and the usual supportive measures. They used gold in half the cases but were unable to assess its value. Of the 28 patients 12 recovered completely, 6 had mild residual joint deformity, 5 moderate or severe residual deformity, 2 died, and 3 still had active disease. *R. S. Illingworth.*

"Rheumatoid Disease" with Joint and Pulmonary Manifestations. ELLMAN, P., and BALL, R. E. (1948). *Brit. med. J.*, **2**, 816.

The authors describe 3 patients with early active rheumatoid arthritis who subsequently developed pulmonary lesions. Two patients died and necropsy revealed interalveolar fibrosis and cellular infiltration with polymorphonuclear leucocytes, mononuclear cells,

and lymphocytes. The lungs were congested, firm, and showed evidence of terminal bronchopneumonia, with minute abscess formation, suggesting " fibrosing pneumonitis ". These changes are compared with the three successive stages of " rheumatic pneumonia " : (1) fibrinoid necrosis in the collagen ; (2) infiltration with round cells, plasma, and giant cells ; (3) fibroblastic proliferation and fibrosis. There was no clinical or necropsy evidence of tuberculosis or sarcoidosis. In the third case there were changes in the *x*-ray picture which were interpreted as favouring a diagnosis of polyarteritis nodosa. In all 3 patients the joint lesions preceded the pulmonary lesions, and the authors assume that both are manifestations of one and the same pathological process, which is presumably a hypersensitivity phenomenon.

[Although the authors state that the joint lesions preceded the pulmonary lesions, it is interesting to note that the first patient had pleurisy and pneumonia at the age of 11, and that the second had previously had recurrent attacks of bronchitis.] *David P. Nicholson.*

Rheumatoid Arthritis. Findings in 136 Cases. (Artritis reumatoide. Revision de ciento treinta y seis casos.) LOSADA, M., and FRANCE, O. (1948). *Rev. clín. esp.*, **31**, 169.

This is a statistical survey of 136 cases of rheumatoid arthritis admitted between 1938 and 1947 to the Hospital del Salvador in Santiago de Chile. Although there are twice as many beds for males as for females in the hospital, 44 of the patients were men and 92 women.

[The paper should be consulted for statistical data.] *A. Lilker.*

Chronic Inflammatory Rheumatism and Focal Infection. Experience in 136 Cases of Rheumatoid Arthritis and 53 Cases of Rheumatism due to Focal Sepsis. (Reumatismos crónicos inflamatorios e infección focal. Experiencia en ciento treinta y seis casos de artritis reumatoides y en cincuenta y tres casos de reumatismos sépticos focales.) LOSADA, M., and FRANCE, O. (1948). *Rev. clín. esp.*, **31**, 176.

In 53 out of 136 cases of rheumatoid arthritis (see above abstract) foci of infection were found and dealt with, without any improvement which could be ascribed to their removal. The authors express the opinion that " the focal infection does not seem to play any important role in the aetiology of rheumatoid arthritis ". Nevertheless they admit the existence of an entity called " focal rheumatism ", and suggest the following criteria for its diagnosis : (1) previous or actual existence of a focus ; (2) lack of predilection for sex, age, or constitutional type ; (3) onset frequently acute or subacute, although sometimes insidious ; (4) general health little or not affected ; (5) absence of trophic cutaneous manifestations and of the muscular syndrome ; (6) few joints, and generally only the great joints, are affected, without tendency to symmetry ; (7) positive intradermal reactions to germs proceeding from the foci ; (8) favourable effect of focal treatment and of pyrotherapy associated with antibiotics. *A. Lilker.*

Gold Therapy of Chronic Joint Disease. (Contributo alle conoscenze sulla crisoterapia delle atropatie croniche.) MASTURZO, A. (1949). *Arch. Patol. clin. Med.*, **27**, 1.

This work consists of 2 sections : (1) a statistical study of the results of gold therapy, based on treatment of 500 cases in 15 years and with special reference to the erythrocyte sedimentation rate (E.S.R.) ; (2) a study of the leucocytosis produced by the injection of gold salts into patients fasting and at rest before, and at hourly intervals for 12 hours after, the injection.

The results are tabulated and graphed. In the cumulative graph obtained by plotting the percentage frequency of improved cases of rheumatoid arthritis against the E.S.R., the majority of improved cases are seen to be those with an E.S.R. of 100 to 110 mm. Westergren in 24 hours. In the second section, the graphs have as abscissae the times of observation, and as ordinates the leucocyte count per c.mm. From the primary curve, a derivative curve and an integral curve were constructed. The primary curve reveals first a leucopenia and later a leucocytosis. Moreover, the leucocytosis almost always occurs after the first injection but not if the dose is inadequate.

In the data below, the term " cure " implies recovery of function, disappearance of pain, complete or almost complete return to normal appearance, and confirmation of return to normal by laboratory reports ; " improvement " implies complete or partial freedom from pain with persistent though lessened limitation of function and some return to normal in the E.S.R. and other reactions. There was improvement in 50% of cases of rheumatoid arthritis, 23% of cases of " vertebral brachialgia ", 40% of cases of spondylitis, 40% of cases of gout, 39% of cases of arthritis of the hip, 33·4% of cases of sciatica, and 27·4% of cases of scapulo-humeral periarthritis. The greatest percentage of cures occurred in scapulo-humeral periarthritis (24·7%), and the lowest in spondylitis (6%). The percentage of cure in rheumatoid arthritis was 10%. The greatest number of failures was obtained in cases of arthritis of the hip. In most cases improvement or cure took place in less than 1 year from the onset, while failure was recorded in most cases treated more than 5 years from the onset. Tables show the greater effect of large doses (100 to 200 mg.) and alternating doses. In most cases of improvement or cure the E.S.R. was high (approximately 100 mm. Westergren in 24 hours) at the commencement of treatment. A dose of 100 to 150 mg. of gold salt is required to affect the white cell count. Cases in which leucocytosis is induced respond more favourably to treatment. The total dose in each course of injections should be 1 to 2 g. The leucocyte count after injection and the E.S.R. furnish data of value in assessing the probable value of gold therapy. *F. Houston.*

Metabolism, Toxicity, and Manner of Action of Gold Compounds in the Treatment of Arthritis. VIII. The Effect of BAL and Other Thiol Compounds in Preventing the Inhibition of Oxygen Consumption of Rat Tissues Produced by Gold Salts. BLOCK, W. D., GEIB, N. C., and ROBINSON, W. D. (1948). *J. Lab. clin. Med.*, **33**, 1381.

BAL had been shown to be of clinical value in treating gold toxicity in human beings. Consequently, it was thought to be of interest to see whether BAL, or other thiol compounds, would prevent the inhibition of oxygen consumption by rat liver and kidney slices produced by the inorganic salts, gold chloride and gold sodium thiosulphate.

Each of the following six thiol, or potential thiol, compounds was assessed : thiomalic acid ; 2 : 3-dimercaptopropanol (BAL), cysteine, sodium thioglucose, L-cystine, and methionine. None of the compounds tried was very effective in preventing the inhibition

of oxygen consumption caused by gold sodium thiosulphate, but all except cysteine and methionine were fairly effective against gold chloride.

P. A. Nasmyth.

The Treatment of Chronic Polyarthritis with Copper Salts. (Chronicus polyarthritisek kezélese rézsókkal.) DIVENYI, A. (1948). *Orv. Lapja*, **4**, 1210.

The author has treated 133 cases of chronic polyarthritis with copper salts since 1943. The copper salt is injected intravenously twice weekly, an initial dose of 0·025 g. being followed by doses of 0·05 to 0·075 to 0·1 g. These doses are increased, when tolerated, to 0·15 g. in the latter part of the course. The course lasts for 7 to 8 weeks, and the total amount injected varies from 1 to 1·6 g. in one course. The course can be repeated after an interval of 8 to 12 weeks. The author divides his 133 cases into three groups. The first group includes 25 cases of rheumatoid arthritis, 16 cases of infective arthritis, and 9 cases of the Poncet type of polyarthritis, without any evidence of nodules. In 52% of the cases either symptoms disappeared or there was great improvement. In the second group, out of 63 cases of chronic polyarthritis with a septic focus symptoms disappeared or improved in 61%. In the third group, out of 20 cases of subchronic polyarthritis originating from acute arthritis 12 became symptom free and 6 improved, but 2 showed no improvement. It is concluded that copper therapy is superior to gold therapy because (1) it is almost as effective ; (2) it does not lead to complications and therefore can be administered where gold is contra-indicated ; (3) the slight reaction warrants treatment in the early stage (in the subacute or subchronic phase) with or without physiotherapy. The use of copper salts is empirical. The mode of action is still unknown, but it is believed that the effect is similar to that of gold, (*a*) chemotherapeutic ; (*b*) by stimulation of resistance ; (*c*) catalytic. [The type of copper salt used is not given.]

D. Gutmann.

Effect of Blood Transfusion on Rheumatoid Arthritis. SIMPSON, N. R. W., and BROOKS D. H. (1948). *Proc. R. Soc. Med.*, **41**, 609.

The aim of this investigation was to determine the effect of transfusions of whole blood, concentrated red cells, and plasma, on both the blood picture and the general condition of the patients. The results of plasma-protein estimations in 24 cases, both before and after transfusion, and in 5 cases of ankylosing spondylitis are analysed. The authors do not draw conclusions from this small series, but intend to continue these studies with normal controls. They did note, however, that in those cases in which the plasma protein values returned to normal there was a coincident improvement in the general condition of the patient. *W. S. C. Copeman.*

Spontaneous Rupture of Muscle as a Complication of Rheumatoid Arthritis. KERSLEY, G. D. (1948). *Brit. med. J.*, **2**, 942.

This paper describes 2 cases, both in males, of sudden rupture of muscle fibres, unassociated with trauma, occurring as a complication of rheumatoid arthritis. A biopsy performed at the site of the rupture in one case showed very marked degenerative changes in the muscle fibres, with complete disappearance of striation, together with large areas of fibrous tissue but little inflammatory reaction. *S. Karani.*

(Osteo-Arthritis)

Arthritis Deformans of the Hip Joint and its Pathological Histology. Research in Polarized Light. LUGIATO, P. E. (1948). *J. Bone Jt Surg.*, **30A**, 895.

The pattern of the collagenous fibrils of articular cartilage was studied in unstained sections from osteo-arthritic joints by means of polarized light. Disturbance of the normal fibril system is one of the first manifestations of cartilage degeneration, and various appearances of the fibrillar structure, both of cartilage and of bone are described in the different stages of the disease. [No new conclusions are reached ; the technique is not new ; many others have failed to obtain much information by its use.] *Douglas H. Collins.*

Intrapelvic Obturator Neurectomy for the Relief of Chronic Arthritis of the Hip. KEY, J. A., and REYNOLDS, F. C. (1948). *Surgery*, **24**, 959.

Operative treatment for chronic pain in degenerative hypertrophic arthritis is indicated at the stage when conservative treatment is failing to give relief. For over fifteen years one of the authors (J.A.K.) has been dividing the obturator nerves outside the pelvis ; this procedure may be combined with acetabuloplasty (Smith-Petersen). Twenty cases subjected to operation during the past 18 months are reviewed. In 18 unilateral cases intrapelvic obturator neurectomy (Selig) was used, and attention is drawn to the fact that adhesions after a fracture of the pelvis may cause inadvertent opening of the bladder. In two bilateral cases in the series the transverse suprapubic (Pfannenstiel) incision was employed.

It was impossible to determine whether the operation is especially useful in any one type of chronically painful hip. The improvement is due partly to paralysis or weakening of the adductor muscles, but, if there is complete paralysis, weakness and instability of the limb will result. Thus the operation of obturator neurectomy, which must include the posterior division with its sensory branch to the hip, should be reserved for cases of painful chronic arthritis with associated adductor spasm or contracture.

[These authors have been more fortunate than the majority of orthopaedic surgeons. It must be realized that these are only interim results ; review of the series after two years may reveal considerable alteration.]

W. A. Law.

(Spondylitis)

Effect of Roentgenotherapy on Urinary 17-Ketosteroid Excretion in Ankylosing Spondylarthritis. DAVISON, R. A., KOETZ, P., and KUZELL, W. C. (1949). *J. clin. Endocrinol.*, **9**, 79.

These authors reported in 1947 that in all of 13 males suffering from ankylosing spondylitis there was increased urinary excretion of 17-ketosteroids. They now report further studies in 31 males and 4 females, including the effect of *x*-ray therapy. Excretion was increased in all patients. The average amount excreted in normal males is 14 mg. in 24 hours ; in spondylitis the average figure was 26·7 mg. and figures up to 40 to 50 mg. were recorded. Only when there was great exhaustion did excretion fall to low values. After the completion of *x*-ray therapy high levels were still found, although symptoms and signs of the disease had abated. *Kenneth Stone.*

An Analysis of 200 Cases of Ankylosing Spondylitis. SIMPSON, N. R. W., and STEVENSON, C. J. (1949). *Brit. med. J.*, **1**, 214.

An analysis is presented of 200 cases of ankylosing spondylitis. Ankylosing spondylitis and rheumatoid arthritis must still be regarded as separate diseases in spite of some modern American views. The chief evidence for this is : the absence of nodules in every case of spondylitis ; the fact that muscle biopsies in spondylitis have in no instance shown the changes characteristic of rheumatoid arthritis ; the very different protein plasma values in the two syndromes ; and the considerable differences both in the *x*-ray appearances and the permanent deformities. Moreover, it is generally accepted that gold salts are of no value in the treatment of spondylitis of this type. *W. S. C. Copeman.*

(Miscellaneous)

Reiter's Syndrome : Report of Six Cases. COODLEY, E. L., WEISS, B. J., and EGEBERG, R. O. (1948). *Ann. w. Med. Surg.*, **2**, 500.

Six case histories of Reiter's disease are presented together with a review of the [chiefly American] literature. It is found to be a disease of white males ; no connexion with dysentery was observed [as is usual also in Britain. Paronen (*Acta med. scand.* 1948, Suppl. 212), however, reported 344 cases from Finland in only 12 of which there was no history of a previous diarrhoea.]

The authors conclude that fever therapy (for some years now considered in Britain as the only treatment of value for severe cases) merits further trial.

R. R. Willcox.

Intravenous Procaine in the Management of Arthritis. (An Interim Report.) GRAUBARD, D. J., and PETERSON, M. C. (1949). *Conn. med. J.*, **13**, 33.

The results of intravenous procaine infusions are assessed in 22 cases of traumatic arthritis, 110 of osteo-arthritis, and 33 of rheumatoid arthritis. In most cases there were relief of pain and improved mobility, but results were the least satisfactory in the cases of rheumatoid arthritis. It is concluded that intravenous procaine therapy is a safe procedure and may be a useful adjuvant in the management of arthritis.

Kathleen M. Lawther.

Lumbar Pain due to Interspinous Neo-arthrosis. (La lombalgie par néarthrose interépineuse.) FAOULING, L., LEGER, L., and AKHRAS, A. (1949). *Pr. méd.*, **57**, 34.

The authors describe a case of low back pain in a man, aged 59, due to the condition variously alluded to as " interspinous osteo-arthritis ", " Baastrup's disease ", or " kissing spine ". The diagnosis was confirmed at operation, when a neo-arthrosis, lined by fibrocartilage, was found between the spines of the third and fourth lumbar vertebrae. The authors claim that this condition is more common in cases of lumbar pain than is usually imagined, and quote the experience of Baastrup and Franck in evidence. [The figures of the latter are not very convincing.] The authors stress that there is nothing specific in the history or clinical findings to differentiate the condition from other forms of low back pain, particularly those due to early disk lesions or postural lumbo-sacral shearing forces. They therefore advocate a more careful search for the lesion by means of special radiographs, since it is not demonstrable in the routine lateral and anterior views of the spine, and by local, exactly placed injections of procaine into the interspinous ligaments. The value of the latter procedure is particularly stressed. They claim (with Franck and Baastrup) that early lesions consisting of nipping of the interspinous ligaments between the borders of the spinous processes, with resulting local haematoma formation in the ligaments, occur without radiological evidence, and may be diagnosed by this procedure. The spines are said to be abnormally large and long, and the lesion occurs with increased lordosis resulting from occupational stresses, as in porters or draymen. Conservative treatment, physiotherapy, or application of plaster-of-Paris may be effective. If these measures are not successful, complete resection of the affected spines is the operation of choice. *L. B. Blomfield.*

Vertebral Pain of Static Origin (Lumbar and Lumbo-sacral), Painful Static Disequilibrium of the Lumbar Spine and Lumbo-sacral Joint. I. Normal Conditions of Equilibrium in the Vertical Posture. II. Radiological Studies of Lumbo-sacral Statics and Dynamics in the Upright Posture. III. Study of Some Physiopathological problems in Lumbar and Lumbo-sacral Pain of Static Origin. IV. Lumbar and Lumbo-sacral Disequilibrium in the Transverse Plane. Lumbar Scolioses. V. Lumbar and Lumbo-sacral Disequilibrium in the Antero-posterior Plane. Hyperlordoses. Spondylolisthesis and Retrolisthesis. (Algies vertébrales d'origine statique (région lombaire et lombo-sacrée), Les déséquilibres statiques douloureux de la colonne lombaire et de la charnière lombo-sacrée. I. Les conditions normales de l'équilibre dans la station verticale. II. L'étude radiologique de la statique et de la dynamique lombo-sacrée dans la station debout. III. Étude de quelques problèmes physiopathologiques concernant les algies lombaires et lombo-sacrées d'origine statique. IV. Les déséquilibres lombaires et lombo-sacrés dans le plan transversal. Les scolioses lombaires. V. Les déséquilibres lombaires et lombo-sacrés dans le sens antero-postérieur : hyperlordoses. Spondylolisthésis et Rétrolisthésis.) DE SÈZE, S., ROBIN, J., DIJIAN, A., DAVAINE, R., AUQUIER, L., JURMAND, S. H., DURIEU, J., and JAFFRES, —. (1948). *Rev. Rhum.*, **14**, 257.

The anatomical factors in the statics of the lumbo-sacral region are considered. Orthodox clinical examination is described but is held to be subsidiary to radiological examination with the patient in the upright position. The technique is described and illustrated. Methods whereby deviations from the normal may be measured are given.

The mechanical effects and pathological consequences of pressure and traction (as in scoliosis and hyperlordosis) on the articular elements of the spine are described. The parts played by osteophytes, ligaments, and intervertebral disks in the production of pain are assessed.

The causes of lumbar scoliosis in the adult are enumerated and the exact sites of the primary deformities are discussed in detail. The aetiology, symptoms, signs, *x*-ray changes, and treatment of hyperlordosis, spondylolisthesis, and retrolisthesis are described and illustrated.

K. M. Lawther.

Sciatica

The Results of Lumbar Fusion in Disc Degeneration. [In English.] UNANDER-SCHARIN, L. (1948). *Acta orthopaed. scand.*, **18**, 125.

The results are described of clinical and radiographic re-examination of 46 cases of intervertebral disk degeneration treated by lumbar fusion. Only one disk was degenerated in 24 cases, and more than one in 22. In 11 of the cases laminectomy had been performed previously, and in 12 it was carried out at the same time as the grafting. The observation period was over a year in all cases. The subjective results were good in 30, improved in 3, and worse than before operation in 13. Among the patients in whom the results were bad were 9 who had had extensive laminectomy, and 6 with unsatisfactory fusion ; 9 belonged to the group of 22 cases with degeneration of more than one disk. In 4 cases a new disk degeneration developed above the graft.

J. Agerholm-Christensen.

An Attempt to Diagnose the Level of a Disc Lesion Clinically by Disc Puncture. [In English.] HIRSCH, C. (1948). *Acta orthopaed. scand.*, **18**, 132.

Puncture of one or both of the two lower lumbar disks were performed in 16 cases of low back pain resistant to conservative treatment. Increasing the intradisk pressure by the injection of saline solution produced pain indistinguishable from spontaneous pain, and injection of procaine solution gave temporary relief.

J. Agerholm-Christensen.

Clinical Diagnosis of Lumbar Disc Herniations. [In English.] STAHL, F. (1948). *Acta orthopaed. scand.*, **18**, 141.

At the University Orthopaedic Clinic in Lund, 306 cases were explored for suspected lumbar disk herniation. The neurological signs are compared with the findings at operation. Herniation or protrusion was found between L5 and S1 in 167 cases, between L4 and L5 in 117, in both these places in 4, and between L3 and L4 in 2. The findings at operation were negative in 16. More than one neurological sign was present in 25% of the cases, a disturbance of segmental sensibility was the sole neurological sign in about 2·5%, and there was no definite neurological sign in 6·5%. Most of the cases had only one neurological sign indicating the level of the lesion.

A diminished Achilles tendon reflex was the sole sign detected in 129 cases ; in 80% of these a lumbo-sacral herniation was found, in 15% herniation of the 4th lumbar disk, and in less than 5% the operation findings were negative. Paresis of the big toe was the sole sign in 64 cases ; 83% had a herniation of the 4th lumbar disk, 14% of the lumbo-sacral disk, and in 3% operation findings were negative. A diminished knee-jerk was the sole sign in 7 cases ; 4 had herniation of the 4th lumbar disk, 1 of the 3rd, and 2 negative findings.

More than one neurological sign was present in 78 cases, and, of these, 75 showed a herniation (68 cases) or a protrusion (11 cases), 4 having changes in both the lowest interspaces. Two or more interspaces were explored in 29 cases, and a lesion in two interspaces was found in only 4 cases. The commonest combination of signs was a diminution of the Achilles tendon reflex with paresis of the big toe, and in these cases the 4th and 5th disks were involved with equal frequency. Complete absence of the Achilles tendon reflex with varying degrees of paresis occurred in 32 cases : in 20 the lesion was lumbo-sacral, in 11 in the 4th disk, and in 1 in both disks. In most cases both neurological signs were already present at the first examination, but in 20 only one of the signs was present. In 16 impairment of the Achilles tendon reflex was the first sign, and in 12 of these the lesion was lumbo-sacral, in 3 in the 4th disk, and in 1 in both disks. Paresis of the extensors was the first sign in 4 cases : 3 had changes in the 4th disk and in 1 the findings were negative. Objective disturbance of segmental sensation was found in only 28 cases : 22 had lesions of the 5th disk, 5 of the 4th, and only 1 had protrusions in both the lowest interspaces.

Myelography, with a negative contrast medium, was carried out in 115 cases. The findings were confirmed at operation in 60% and were misleading in 40%. The author concludes : " Thus in most cases the clinical signs point to the interspace where the herniation is to be sought, but a negative finding there means that the adjacent space must be explored. A routine exploration of the two lowest interspaces is unnecessary, even in cases with several neurological signs."

J. Agerholm-Christensen.

Juvenile Degeneration of Intervertebral Disks. (La dégénérescence juvénile du disque inter-vertébral.) LAEDERER, R. (1948). *Schweiz. Z. Path. Bakt.*, **11**, 590.

The nucleus pulposus of the intervertebral disk is not vascularized, and the small straight vessels running through the surrounding cartilage usually disappear by the age of 30 years.

The author investigated 50 unselected spines from healthy subjects of all ages. The cut surfaces were closely examined, and sections were prepared. Up to the age of 30 years small foci of necrosis are almost constantly seen in the hyaline cartilage of the disks. Sometimes small centres of " pre-ossification " are seen which are really vessels surrounded by accumulations of cartilage cells. Small protrusions of cartilage into the spongy bone of the vertebrae are fairly frequent, even in adolescence, and might be interpreted as osteochondrosis. It is through these lesions that the nucleus pulposus may herniate. The author believes that the lesions found represent the florid phase of painful juvenile kyphosis or Scheuermann's disease. *E. Neumark.*

The End-results of Surgery for Ruptured Lumbar Intervertebral Discs. A Follow-up Study of 327 Cases. SPURLING, R. G., and GRANTHAM, E. G. (1949). *J. Neurosurg.*, **6**, 57.

This follow-up report covers 8 years, but the more recent cases seem to date back a few months only. Only 80 of the patients were examined ; the results in the other are assessed on a questionary. In this group, the authors stress that the only specific indication for surgery was low back pain and sciatica which was refractory to conservative treatment. The diagnosis was made on clinical grounds ; myelography was considered of value only as a means of location. A complete disk removal was carried out through the usual interlaminar approach ; spinal fusions were not done. The usual post-operative regimen consisted of 10 days' rest in bed, walking at the thirteenth day, and home by the fourteenth day ; sedentary work was resumed at 4 weeks, and heavy labouring at 3 to 6 months. The work of 44% of the patients was considered to be heavy. There were 30 negative explorations. Of those who had low back pain, 40% considered themselves cured and 52·3% had occasional mild attacks of pain. Of those

with root pain in the leg, 46·5% were cured, and 45% had slight residual pain which was not disabling. Of the total, 85·6% were able to return to their previous occupation, and 79% considered that the operation had been successful. In a group of compensation cases (24% of the whole series) 66·6% considered the operation a success. Of the patients in whom exploration was negative, 72% were rendered free from symptoms. These results are ascribed to the extensive root decompression that was carried out.

In the whole series, 40% were considered completely cured, 39·2% were left with slight but not disabling residual symptoms, and 20·8% were considered partial successes or failures. A further operation was done in 21 cases for suspected recurrence. In 10 patients true recurrences were found at the same level ; in 2 lesions were found at other levels. In the remainder the only finding was dense scarring around the affected root.

E. B. C. Hughes.

Plain Radiography in Intraspinal Protrusion of Lumbar Intervertebral Disks : A Correlation with Operative Findings. BEGG, A. C., and FALCONER, M. A. (1949). *Brit. J. Surg.*, **36**, 225.

This is an excellent account of the radiographic changes seen on straight *x*-ray films in lumbar disks. [The original article should be consulted for details. It is to be hoped that the authors will write another paper when they have studied vertebral mobility in a larger series of cases.] *J. W. D. Bull.*

Gout

The Genetics of Gout and Hyperuricemia—An Analysis of Nineteen Families. SMYTH, C. J., COTTERMAN, C. W., and FREYBERG, R. H. (1948). *J. clin. Invest.*, **27**, 749.

In this article the hypothesis is discussed and investigated that gout is caused by a dominant autosomal gene [the gene placed on any chromosome other than the XY or sex chromosome] expressing itself fairly regularly in hyperuricaemia but only occasionally in gouty arthritis. An analysis is given of 19 gouty families. In each case the original patient was a male with clinical, biochemical, and in most cases radiological evidence of gouty arthritis. Altogether 87 relatives were studied. The variation in serum urate levels was studied to ascertain whether the relatives could be divided into " normal " and " hyperuricaemic " groups, in the hope that these would correspond to two specific genotypes.

Despite important individual variations, the frequency diagrams suggested a bimodal distribution of serum urate levels among relatives of both sexes, which were therefore classified on the basis of the minimum points in these distributions—namely, males with over 6 mg. of uric acid per 100 ml. of serum, and females with over 5 mg., were considered hyperuricaemic. The females averaged 1 mg. less uric acid than males—a finding which agrees with that of previous workers. The statistical evidence also appeared to show that males under 16 years of age did not under any circumstances have serum urate levels above 6 mg. If it was assumed that the metabolic change resulting in hyperuricaemia is not manifested in males till about the age of puberty, the data concerning the male relatives was in agreement with the hypothesis of dominant autosomal inheritance. The proportion of hyperuricaemic females was, however, significantly smaller than that expected. It is, therefore, probable that hyperuricaemia is not detectable in some heterozygous females even when a liberal reduction in the critical level for hyperuricaemia is made.

Although gouty arthritis occurs much more frequently in males than in females, the evidence does not suggest the existence of sex-linkage. This is made unlikely by the common occurrence of gouty or hyperuricaemic sons of gouty male patients. With sex-linkage one would also expect higher average urate levels, or a higher incidence of hyperuricaemia, among daughters of hyperuricaemic males than among daughters of hyperuricaemic females. [The results recorded give no suggestion of such a difference.] *R. P. Foggie.*

Non-articular Rheumatism

Herniation of Fascial Fat : A Cause of Low Back Pain. HUCHERSON, D. C., and GANDY, J. R. (1948). *Amer. J. Surg.*, **76**, 605.

The authors confirm the earlier English work of Copeman and Ackerman, who reported in 1944 and 1947 that painful palpable " fibrositic " nodules occurring in certain regions of the back were found to be herniations of fat through the deep fascia.

The present authors believe that herniation of fascial fat is a definite cause of back pain, the demonstration of which has added to our knowledge of this perplexing problem.

Suprascapular Nerve Block : Evaluation in the Therapy of Shoulder Pain. MILOWSKY, J., and ROVENSTINE, E. A. (1949). *Anaesthesiology*, **10**, 76.

This is a study of 100 consecutive patients treated by nerve block for stiff and painful shoulder. Other methods of treating shoulder pain are mentioned and the rationale of suprascapular nerve block is considered. A good result may be expected from a single block in most patients with subacromial bursitis and in those with capsular tears. Results with other lesions are not uniformly successful. *Ronald Woolmer.*

Causation and Treatment of Painful Stiff Shoulder, Subdeltoid Bursitis, Periarthritis, Tendinitis and Adhesive Capsulitis. MEYERDING, H. W., and IVINS, J. C. (1948). *Arch. Surg., Chicago*, **56**, 693.

The authors discuss the pathology of painful stiff shoulder and analyse 150 cases treated at the Mayo Clinic between 1942 and 1946.

General Pathological Articles

The Effect of Para-aminobenzoic Acid on the Metabolism and Excretion of Salicylate. SALASSA, R. M., BOLLMAN, J. L., and DRY, T. J. (1948). *J. Lab. clin. Med.*, **33**, 1393.

A single 3 g. dose of sodium salicylate given by mouth resulted in a peak salicylate level in plasma of 18 to 22 mg. per 100 ml. in 2 to 4 hours. After 28 to 32 hours, the level in plasma had fallen to 1 mg. or less per 100 ml. If, however, 3 g. doses of *para*-aminobenzoic acid were given every 3 hours for the duration of the experiment, beginning 18 hours before the administration of sodium salicylate, the maximum concentration of salicylate in the plasma was again obtained 2 to 4 hours after its administration, but was still approximately 5 mg. per 100 ml. 55 hours later.

In an attempt to determine the mechanism of this

phenomenon, estimations of the plasma salicylate and urinary salicylates were made at different time intervals over a period of 60 hours. The results obtained showed that most of the sodium salicylate is normally excreted as salicyluric acid in man, but that when *para*-aminobenzoic acid is given with it the combination of the salicylate with the glycine in the liver is inhibited, and the urinary excretion of salicyluric acid is therefore very much reduced. The excretion of free salicylate and salicyl glycuronates is somewhat increased in these circumstances, but this does not compensate for the fall in the excretion of salicyluric acid. At no time was there a retention of salicyluric acid in the blood, and it was shown that *para*-aminobenzoic acid greatly reduced the formation of hippuric acid from sodium benzoate in the liver function test. The administration of exogenous glycine did not eliminate this latter effect.

The *para*-aminobenzoic acid did not affect the excretion of salicylates in dogs, in which there is no conjugation with glycine in the liver. *P. A. Nasmyth.*

Differential Diagnosis of Rheumatoid Arthritis by Biopsy of Muscle. STEINER, G., and CHASON, J. L. (1948). *Amer. J. clin. Path.*, **18**, 931.

Biopsy specimens were taken from the gastrocnemius and deltoid muscles of patients suffering from rheumatoid arthritis and a variety of other conditions associated with inflammatory changes in muscles. Sharply circumscribed aggregations of lymphocytes, surrounded by an outer layer of plasma cells, situated in the endomysium, and/or perimysium, but only very rarely in the epimysium were found almost constantly in cases of rheumatoid arthritis. Only in 1 out of 7 patients suffering from lupus erythematosus was the histological picture so similar that the two conditions could not be differentiated, though at necropsy, some time later, this was again possible. In no other condition were intramuscular, sharply defined nodules, consisting solely of lymphocytes and plasma cells, present. *R. Salm.*

The Pathogenesis of Rheumatic Allergy. (К патогенезу ревматической аллергии.) VOROBYEV, I. V. (1948). *Klin. Med., Mosk.*, **26**, No. 11, 3.

A review is given of several years' study of allergy in acute rheumatism, with reference to 110 patients. The local, focal, and general reactions to intradermal injection of 0·1 ml. of a vaccine containing 100,000,000 streptococci were observed.

Haemolytic Streptococcus Agglutination and Antistreptolysins in Rheumatoid Arthritis. (Streptococcagglutination og antistreptolysintiter ved polyartritis chronica primaria.) PORSMAN, V. A. (1948). *Nord. Med.*, **40**, 2147.

Streptococcal antihaemolysin and agglutination titres were determined in 102 patients suffering from rheumatoid arthritis. A positive agglutination reaction was found in 61 patients ; positive reactions were commoner in patients who had had rheumatoid arthritis for more than a year. Considerable variation in titre was found in determinations repeated after varying intervals ; this was perhaps due to the effect of sanocrysin treatment. The antistreptolysin titre was raised in 17 patients. The results of the investigation show no significant departure from normal values, and do not support the theory that rheumatoid arthritis is due to streptococcal infection. *D. J. Bauer.*

Visceral Lesions in a Case of Rheumatoid Arthritis. GRUENWALD, P. (1948). *Arch. Path.*, **46**, 59.

A man of 57 had a 6-year history of crippling rheumatoid arthritis. At necropsy the heart (320 g.) showed ischaemic fibrosis. In the right atrium there were many small (2 mm.) yellowish nodules. There was also one nodule $10 \times 10 \times 5$ mm. in the substance of the tricuspid valve. The pleurae and pericardium and splenic capsule were thickened. Histologically the atrial nodules were of the same structure as the subcutaneous nodules of rheumatoid arthritis. The centre was necrotic but special staining showed it to have been collagenous ; this was surrounded by an inner zone of radially arranged histiocytes amongst which were a few giant cells, lymphocytes, and polymorphonuclear cells. Outside this was a second zone of indifferent granulation tissue. The nodule in the tricuspid valve was similar and there were also similar lesions in the pleurae and splenic capsule, though in these sites the lesions were more diffuse and less strictly nodular. The authors claim that lesions of this rheumatoid type, as opposed to rheumatic ones, have not previously been reported at these sites, and they regard them as important in indicating the widespread nature of rheumatoid arthritis. [These rheumatoid nodules with necrotic centres should not be confused with the Aschoff type of nodule seen in ordinary rheumatic carditis and not infrequently also in the heart in cases of rheumatoid arthritis.] *C. V. Harrison.*

The Hyaluronic Acid of Synovial Fluid in Rheumatoid Arthritis. RAGAN, C., and MEYER, K. (1949). *J. clin. Invest.*, **28**, 56.

The authors investigated the synovial fluid obtained at necropsy from the knee-joints of 11 controls, and 35 patients with rheumatoid arthritis. Hyaluronic acid concentration was measured by the method of Meyer (*Physiol. Rev.*, 1947, **27**, 335). Viscosity was determined by the method of Ragan (*Proc. Soc. exp. Biol., N.Y.*, 1946, **63**, 572). The fluid was diluted with 0·85% saline. The exponential curve derived by plotting the logarithm of the viscosity of the synovial fluid or pure sodium hyaluronate against the dilution is a straight line. There is thus a straight-line relation between log viscosity and concentration of hyaluronic acid, and the quotient derived from the division of these two factors is a constant irrespective of the dilution of the synovial fluid by extracellular fluid. The increased viscosity of synovial fluid is due to hyaluronic acid, and the viscosity is an index of the polymerization at a given concentration : this quotient gives the mean polymerization of the hyaluronic acid present in a sample of fluid.

The quotient was found to be less than 10 in the 35 cases of rheumatoid arthritis and above 10 in the controls. It is said to bear a direct relation to the severity of the disease. In 4 " burnt-out " cases, with resultant deformity of long duration, the quotient was above 10, and in cases of remission or " smouldering ", with few general signs, it was above 8·10. With quotients below this level patients showed fatigue, loss of weight, and fever. The concentration of hyaluronic acid was the same as in controls, but because of the greater volume present in rheumatoid arthritis the total amount in this disease was greater.

The authors conclude that the hyaluronic acid present in the synovial fluid in rheumatoid arthritis is less highly polymerized, and that this change is parallel to the changes in this mucopolysaccharide in the connective

tissues of the remainder of the body. They regard this as a primary lesion in rheumatoid arthritis and, since hyaluronidase is lacking in the joint and synovial structures, regard the mechanism as a failure of synthesis.

[No findings are given for infective conditions, other forms of arthritis, or joint trauma. The hyaluronic acid source is very problematical, the acid being possibly concerned with osmotic pressure and the defensive mechanism of joint, by which it may be formed. It is formed by capsules of streptococci. The amount varies from joint to joint, and with disease processes in joints.]

L. B. Blomfield.

Pathogenesis of So-called Diffuse Vascular or Collagen Disease. YARDUMIAN, K., and KLEINERMAN, J. (1949). *Arch. intern. Med.*, **83**, 1.

Five cases are described with clinical, chemical, and post-mortem data—one each of lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, generalized visceral thrombo-angiitis obliterans, and scleroderma. The vascular lesions are considered as examples of " accelerated ageing ", the primary affection being of the small arterioles and capillaries. The varied histological pictures are said to be dependent " on the type, intensity, and constancy of noxious agents and the individual healing response ". The authors maintain that the appearances they describe are common to the group.

A. C. Lendrum.

Histological Changes in the Brain in Experimental Rheumatism (Anaphylactic). (Alteraciones histológicas cerebrales en el reumatismo experimental (anafiláctico).) MALLEN, M. S., COSTERO, I., and HUBE, E. L. (1948). *Arch. Inst. cardiol. Mex.*, **18**, 688.

The authors studied the cerebral and myocardial lesions of experimental rheumatism and compare their findings with those in human acute rheumatism. Rabbits were given three subcutaneous injections of 2 ml. of normal horse serum at 48-hour intervals. Four weeks later the animals were given a dose of 2 ml., and were killed after 3 days. Of the 16 test rabbits, 4 showed proliferation of microglia round blood vessels ; in 2 of these, evidence of annular haemorrhages with pericapillary necrosis was seen, and one of them had dilatation of the lymphatic spaces. Animals were killed too soon after the induction of shock for the capillary sclerosis described by German workers to be observed. Since the changes are similar to those found in human acute rheumatism, the authors maintain that the human lesions also have an allergic character.

George Hickie.

Other General Articles

Referred Pain and Associated Phenomena. SINCLAIR, D. C., WEDDELL, G., and FEINDEL, W. H. (1948). *Brain*, **71**, 184.

The authors review the literature and conclude that there are two " opposing views " concerning the phenomenon of referred pain. The first is that some mechanism located centrally is responsible ; the other that the phenomena are produced by events at the periphery. They conclude that neither hypothesis explains all the observed facts. They then review the experimental work and expound a theory dependent on the existence of axon branching. In view of the frequent existence of axon branching in other mammals, the supposition that this particular arrangement might also occur in man is not unwarranted.

Arguing from the experimental production of referred pain by saline injection near the dorsal nerve trunks lying near the interspinous ligaments, the authors suggest that impulses arising in the territory of the posterior division and in the anterior division must occasionally find themselves in joint possession of a single " final " pathway to the pain-receiving centre. If it be assumed that the centre is incapable of distinguishing the ultimate source of the impulses reaching it by these common pathways it becomes possible to explain how stimulation of one branch of such an axon might give rise to the sensation of referred pain in the district served by the other branch. It may be assumed that such bifurcating axons are relatively infrequent, which could explain why referred pain seldom arises from stimulation of the skin or deep tissues whereas it does from stimulation of a nerve trunk. If the sister branches are scattered at random within the territory then they are probably isolated from each other, which would explain the imperfect localization and unpleasant character of referred pain. The production of cutaneous hyperalgesia is explained by the liberation of a metabolite at the nerve endings as a result of antidromic impulses passing down the cutaneous limbs of the branched axon systems. It is further suggested that the other branch of the axon may terminate not in the skin but in deep tissues, so giving rise to phenomena of referred deep tenderness. Anaesthetizing the area of reference will abolish the metabolic element but leave unchanged the element of central misinterpretation.

By suggesting that branched axons exist, having one limb supplying a viscus and the other skin or deep somatic tissue, the authors expand their theory to cover referred pain from visceral structures. They even suggest tentatively that a reference by stages may be possible ; the branched axon from a viscus causes appearance of a metabolite in a muscle which, by affecting a second branched axon, might lead to the production of a similar disturbance in an area of skin. *N. S. Alcock.*

Studies in Low Backache with Persistent Muscle Spasm. PRICE, J. P., CLARE, M. H., and EWERHARDT, F. H. (1948). *Arch. phys. Med.*, **29**, 703.

Patients with low backache were studied. Areas of tenderness in the back were mapped out, and the pain was found to vary in intensity and position from day to day and from patient to patient. A series of electromyograms was taken, recording the activity in the muscles of the back during test positions and movements. Patients with backache were found to have patterns of muscular activity differing from the normal. Diagrams correlate the position of tenderness with the electromyographic findings. In the acute stage the patients were treated by heat, massage, faradism, and gentle movement. In the chronic stage any residual postural deformity was corrected by relaxation, light exercise, and special rhythmic movements. Patients who achieved good relaxation attained relief from pain. *J. H. Cyriax.*

Metastatic Calcification. Is the Role of Hypercalcemia over-emphasized as a Toxic Manifestation of Vitamin D Therapy in Rheumatoid Arthritis ? COHEN, A., REINHOLD, J. G., and COHN, R. (1948). *Industr. Med.*, **17**, 442.

The authors give details of serum calcium levels found in 47 of 150 patients suffering from rheumatoid arthritis and treated with large doses of vitamin D and conclude that the risks of intensive vitamin D therapy are not as great as they are generally believed to be. They advocate the careful selection of patients who are to receive

vitamin D in order that those in whom contra-indications exist should not be treated with it. They also advocate a careful watch for early signs of toxic manifestations. They suggest that prolonging vitamin D therapy beyond one year may be inadvisable. *W. Tegner.*

Titles of other Articles in the Current Literature

Therapeutic Criteria in Rheumatoid Arthritis. (A summary of the recommendation of the Committee for Therapeutic Criteria of the New York Rheumatism Association proposing the adoption of uniform systems of classification of the stages of progression, degree of functional impairment, and response to treatment.) STEINBROCKER, O., TRAEGER, C. H., and BATTERMAN, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

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Treatment of Chronic Rheumatic Diseases with Synthetic Oestrogens. (Traitment des rhumatismes chroniques par les oestrogènes de synthèse.) HOCHFELD, M. (1949). *Progr. méd., Paris*, **77**, 219.

Bilateral Hydrarthrosis of the Knees in Girls and Its Treatment with Testosterone (L'hydrarthrose bilatérale des genoux chez la jeune fille et son traitement par la testostérone.) LEDERER, J. (1949). *Rev. Rhum.*, **16**, 196.

Synthetic Oestrogens in Treatment of Degenerative Rheumatism. (Les oestrogènes de synthèse dans le traitement des rhumatismes chroniques dégénératifs.) WEISSENBACH, R. (1949). *Bull. méd., Paris*, **63**, 183.

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THE HEBERDEN SOCIETY

An ordinary meeting of the Heberden Society was held on Oct. 7 at the Postgraduate Medical School of London. Dr. W. S. C. Copeman took the chair, and thirty-six members and guests were present.

Dr. L. G. C. Pugh gave a short paper on temperature gradients and blood flow in the limbs and the effect of local application of cold. The idea, prevalent since the time of Lefèvre (1911), that all the tissues deep to the skin were maintained at a constant temperature near 37° C., was no longer acceptable. The distribution of temperature in different regions of the body showed considerable variation. Among the factors determining the temperature in different regions was the surface volume ratio : large limb segments such as the thigh had different temperature gradients from smaller segments, such as the arm. In the resting subject about 70 per cent. of the body heat was produced in the liver and intestines, and only 15 per cent. in the muscles. This information had been gained by measurement of blood flow to the liver and intestines, and the temperature difference between hepatic venous blood and right ventricular blood. Total heat production in the resting muscle had been calculated from measurement of the oxygen consumption on resting forearm muscle. This was done by measurement of the forearm blood flow and arterio-venous oxygen difference. During exercises, on the other hand, the main site production shifted from the centre to the periphery. This fact might turn out to be important in connexion with the differences in cold tolerance between fat and thin people. For instance the Channel swimmer, Mickman, a short, fat, subject, remained twenty-two hours in the Channel, whereas a thin person was usually unable to tolerate immersion in water of this temperature for more than half an hour.

It might be supposed that in subjects with little subcutaneous tissue muscle, heat was drained away at the site of its production, whereas in people with a relatively thick layer of subcutaneous fat the heat generated in the muscles was available for maintaining general body temperature. Slides were shown illustrating the rapid increase in temperature in the arm during exercise. These results were obtained by passing a fine wire containing a thermo couple through the arm. This permitted direct measure of muscle temperature during exercise.

Dr. Pugh discussed the effect of local cold on tissue temperature and blood flow. He showed that within twenty minutes of immersing the forearm in water at 17° C. the deep muscles cooled from 35° to less than 25° C., and the forearm blood flow had fallen from 3½ ml. per 100 g. tissue per minute to less than 1 ml. per 100 g. tissue per minute, in fact a mere trickle. He showed that the blood flow was not significantly increased by a sympathetic nerve block, and said that it was fairly well established that the blood vessels were directly sensitive to cold, and constricted independently of impulses from the autonomic nervous system.

The significance of this kind of work for rheumatology depended on the fact that the structures affected in rheumatic diseases were relatively superficial and, therefore, subject to the direct influence of changing environmental temperature.

The meeting then took the form of clinical demonstrations by Dr. E. G. L. Bywaters and other members of the Staff, followed by discussion.

Case 1 (presented by Dr. E. G. L. Bywaters) was a woman of 53, with arthritis mutilans (*main-en-lorgnette*) whose joint symptoms followed deep *x* radiation fifteen years previously for a condition diagnosed as secondary carcinoma of the lungs. The lung fields were now in the same state as they were then, and consisted of multiple large opacities. There were in addition large, sharply-defined areas of rarefaction in the skull and in one rib, a wedge-shaped vertebral collapse, and a pigmented patch on the abdomen. The high alkaline phosphatase argued a general disorder of bone ; and the group syndrome including Hand-Schüller-Christian, Albright's syndrome, and eosinophilic granuloma was put forward as a possible diagnosis. It was not felt, however, that xanthomatous infiltration had anything to do with the joint disorder (as in Graham's case), since the joint and bone biopsies that were demonstrated showed the changes of rheumatoid arthritis. Nor, despite the general similarity to Layani's case, was the blood cholesterol raised.

Similar views were brought forward in the discussion by Dr. Highton and others, although Dr. Bywaters felt that lung opacities never reached this size in granulomatous disorders.

Case 2 (presented by Dr. E. G. L. Bywaters) was a case of chronic post-rheumatic joint deformity of the type described by Jaccoud in 1867. It was not thought to be rheumatoid despite the marked ulnar deviation since the biopsy which was demonstrated showed only capsular fibrosis and the blood sedimentation rate was normal. Attention was drawn to the bony erosions, similar to those seen in Bach's (1935) case. The syndrome was rare, although Dr. Bach said he had at present a somewhat similar case, Dr. Lush mentioned a case under the care of Professor Hartfall, and Dr. Bywaters spoke of another case seen in Walter Bauer's Clinic.

Case 3 (presented by Dr. L. G. C. Pugh) was one of Sjögren's syndrome in an elderly woman with rheumatoid arthritis. Deficiency in lachrymal secretion was shown to be an accompaniment of advancing years, particularly in men. Other deficiencies, including those of salivary, gastric, and intestinal secretions, and sweat, and the methods adopted to measure them quantitatively were then described. On a sweating test the patient showed an unusual rise of temperature, which demonstrated the lack of normal temperature regulation by this means.

Dr. Pugh said that vaginal secretion had not been measured, but that it was known to be deficient in other cases.

Case 4 (presented by Dr. E. G. L. Bywaters and Dr. Graham Bull) was a woman who attended an orthopaedic and then a rheumatism clinic for pain in the knees, and who showed mild degenerative changes on *x*-ray examination and a normal erythrocyte sedimentation rate. When other bones were found to be tender, serum calcium

phosphorus and phosphatase determinations showed values consistent with hyperparathyroidism, and *x*-ray examination of other bones confirmed this diagnosis.

Dr. Bull then demonstrated the biochemical changes before and after the removal of a parathyroid adenoma, together with electrocardiographic changes and specific changes in the renal clearance of phosphate ion. It was emphasized that such cases, although rare, made it necessary for people interested in joint disease or kidney disease to be conversant with general medicine rather than to become narrow specialists.

Case 5 (presented by Dr. Wild and Dr. L. G. C. Pugh) was a man with rheumatoid arthritis treated with ACTH. The remarkable subjective improvement on the third day of the active therapy was demonstrated, and the methods by which it was hoped to secure evidence of the potency of the preparation and its objective effects upon joint physiology and biochemistry were outlined. A brief review was given of the general plan of the therapeutic trial.

Case 6 (presented by Dr. E. Dresner) was a man who had been treated by venesections for well authenticated polycythaemia vera. He developed acute joint symptoms, and on admission to the Postgraduate Medical School was found to have myeloid leukaemia and a serum uric acid of 13 mg. per 100 c.cm. of blood. The differential diagnosis between gout and rheumatoid arthritis was discussed, and it was concluded, largely because of the clinical pattern, the development of a biopsied ear tophus, and the well-known association with leukaemia, that this was a case of gout.

In discussion it was suggested that an investigation of other members of the family would be helpful. It was remarked that any form of tissue degeneration in a patient with a raised uric acid would show uric acid crystals even if the focus was a rheumatoid nodule.

The Librarian of the Heberden Society is anxious to collect books on rheumatism, arthritis, and gout, of historical and scientific interest published before 1900. Any offers by members of the Society or others would be welcomed. They should be made in the first instance to the General Secretary of the Heberden Society, c/o The Empire Rheumatism Council, Tavistock House North, Tavistock Square, London, W.C.1.

NEW YORK RHEUMATISM ASSOCIATION

The Fall Meeting of the New York Rheumatism Association took place on November 9, 1949, at the Cornell University Medical College. Dr. Edward F. Hartung, of New York, was chairman.

The subject discussed was " The Influence of Endocrine Glands on Gout " by Dr. William D. Robinson, Director, Rackham Research Unit, and Associate Professor of Medicine, University of Michigan School of Medicine.

Dr. Robinson stressed the sex difference in the incidence of gout, emphasizing the predominance of male sufferers. Gout in females is uncommon before the menopause. The blood uric acid levels are higher in normal males than in normal females. The blood uric acid levels in non-gouty relatives of gouty patients are also higher in males than in females, but higher levels than usual are found in those females who have passed the menopause. In young children, no difference is found in blood uric acid levels between males and females. In older children, higher blood uric acid levels are found in the males. Uric acid clearance studies show normal males to have less clearance than females.

Age and sex differences in uric acid blood levels and clearance probably depend upon androgen activity. Androgen given to normal children causes a prompt fall in urate clearance. Paradoxically, low excretion of 17-ketosteroids is found to be present during gouty attacks. No change in excretion is noted during attacks in either males or females. Gouty patients have been shown to have low 17-ketosteroid excretion between as well as during attacks. A possible explanation of this paradox is that in gouty patients an abnormal androgen is secreted by the adrenal, which maintains normal androgen function but gives low 17-ketosteroid excretion.

The main hormones of the adrenal cortex may be divided into three groups: (1) sex-like; (2) 11-oxysteroids (including cortisone); (3) desoxycorticosterone-like. The pituitary probably acts on the adrenal cortex by way of adrenocorticotropic hormone (ACTH). The hypothalamic centre of the brain may act on the anterior pituitary by both humeral and neural mechanisms. Stress and epinephrine can stimulate the hypothalamus.

Indices of adrenocortical function of the sex-like hormones are the urinary 17-ketosteroid excretion and a positive nitrogen balance. 11-oxysteroid function is determined by a negative nitrogen balance, depressed carbohydrate metabolism, increased urate excretion, and decreased circulating eosinophiles. Desoxycorticosterone-like activity is determined by study of sodium chloride and water retention, and loss of potassium.

The administration of ACTH to a normal male causes an increased water retention, a negative nitrogen balance, an increased excretion of 17-ketosteroids, a diabetic type of carbohydrate tolerance curve, retention of fluid and electrolytes. The administration of insulin at the same time counteracts the carbohydrate metabolic disfunction, but does not change the urate excretion. Several days after ACTH is stopped, the urate blood level continues to fall; then a " rebound " is noted, at which time the urate level suddenly rises.

The administration of ACTH during gouty attacks causes prompt relief of symptoms. There is an unusual urate excretion and a fall in blood urate level. The other effects are the same as those seen in the normal male, such as increased 17-ketosteroid and potassium excretion, and water retention. The " rebound " phenomenon, however, does not occur in gouty patients. Several cases of recurrence of gouty attacks occurred after cessation of treatment with ACTH, at the same time as the " rebound " occurs in the normal.

Attempts to treat gouty attacks with epinephrine, through hypothalamic stimulation, were unsuccessful.

Colchichine probably does not act through the mechanism of ACTH. Colchichine does not prevent the endocrine effects of ACTH withdrawal, but can prevent and ameliorate post-ACTH attacks. Gouty attacks not responding to ACTH have responded to colchichine.

Gouty patients have an endocrine defect both during and between attacks. ACTH in some way affects purine metabolism, to relieve gouty attacks. The adrenals of gouty patients are able to respond to ACTH in a manner similar to normal subjects, but exhibit no " rebound " phenomenon. Attacks of gouty arthritis occur in patients with gout during periods of decreased adrenocortical function.

BOOK REVIEW

Ankylosing Spondylitis : A Practical Guide to its Diagnosis and Treatment. Part I by F. Hernaman-Johnson, M.D., F.F.R., D.M.R.E. Part II by W. Alexander Law, O.B.E., M.D., F.R.C.S. 1949. London : Butterworth. Pp. 200. Illustrated. Price 25*s*.

It is to be regretted that Dr. Hernaman-Johnson did not live to see the publication of this book, which is the outcome of his wide experience in the diagnosis and treatment of ankylosing spondylitis. The authors state in the preface that their aim has been to present a practical guide, not lacking in details, to the treatment of the disease in all its stages, and in this they have achieved success. To the general practitioner it will be of great assistance, and it may help him to make a correct diagnosis at a stage when the disease can be arrested, and not when serious damage has already been done.

The importance of the pre-spondylitic stage is stressed, the early symptoms are described, and the value of *x*-ray examination in all cases of vague and often intermittent rheumatic pain is made clear. Aetiology and pathology are fully discussed, and the clinical description of the disease in its various stages is clear and vivid and illustrated by excellent radiographs. The method of treatment by means of *x* radiation is very fully dealt with, and Dr. Hernaman-Johnson's long practical experience of radiotherapy makes this section of special value ; it will be read with profit not only by the family doctor, who sees the disease in its earliest stages, but also by those who have had more extensive experience in its management.

The author deals fully with other methods of treatment and, though Dr. Hernaman-Johnson's views on the value of vaccines and gold in spondylitis are not shared by many others, they deserve careful consideration. The reviewer recalls the observation of an eminent rheumatologist that, though he had little confidence in vaccines as a specific treatment in rheumatic diseases, he used them as a means of keeping the patient under close observation. If vaccines are used in the way described in this book they can do no harm, and good is not unlikely to result even if specific action is unlikely. Drugs receive due consideration, together with practical advice on physical methods of treatment, and their importance are fully described by both authors.

The second part of the book, by Mr. Alexander Law, describes the surgical treatment in detail and is a valuable contribution to the subject, which is as yet in its infancy but which nevertheless has been brought to a high degree of technical skill based on the work of Smith-Petersen of Boston, U.S.A. The operative measures for the treatment of spinal deformity are described in detail, with admirable illustrations, and the advice given on after-treatment and physiotherapy in general will be read with profit by all who have to treat these distressing cases.

The book is excellently produced, and the illustrations are of high quality. It is a valuable contribution to the literature of the disease and deserves wide circulation. It is only to be regretted that Dr. Hernaman-Johnson will no longer be able to add to our knowledge of the treatment of spondylitis and of kindred subjects.

C. W. BUCKLEY.

INDEX TO VOLUME VIII

INDEX TO ABSTRACTS

AUTHORS OF ARTICLES ABSTRACTED

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